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Research Article

NARRATIVE REVIEW OF NON-CANCER DISEASE FROM EXPOSURE TO LOW-LEVEL IONIZING RADIATION

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ABSTRACT

Exposure to low-dose ionizing radiation has demonstrated to be associated with a certain risk of cancer but also non- cancer disease. However, only recent, high-quality, individual dosimetry data allowed this risk to be estimated. A correlation between low-dose exposures and various types of non-malignant diseases has only recently been suspected in Japanese atomic bomb survivors, liquidators of Chernobyl accident and various occupationally exposed cohorts and is still controversial. Data on excess relative risks per dose unit for moderate- and low-dose exposure from epidemiological studies are variable, possibly resulting from confounding factors and effect-modification by well known (but unobserved) risk factors. In the present work, we summarized the current evidence for a casual association between chronic, low-dose level radiation exposure and possible effects on embryo and fetus, heart and vessels and brain.

INTRODUCTION

There is a worldwide increasing interest in cumulative ionizing radiation exposure, since recent studies suggest low-dose ionizing radiation (LDR) exposure, other than high-dose one for professional and or medical use to be associated with a significant risk of cancer and non-cancer disease. To date, several categories of people are currently exposed to more LDR, so much so that the International Commission on Radiological Protection (ICRP) judges, in its 2012 recommendations on the basis of existing evidence, that acute doses up to around 0.10 Gy produce no functional impairment of tissues. This includes the lens of the eye regarding the risk of cataract, with the caveat that the use of a threshold model remains uncertain for this tissue. Hence for most applications of ICRP recommendations in occupational or public situations, the stochastic risks of induced cancer and hereditary effects remain the principal risks to consider. At higher doses, the risk of tissue reactions (deterministic effects) becomes increasingly important, particularly regarding radiation incidents and accidents, and medical exposures. (1).

According to the United Nations Scientific Committee on the Effects of Atomic Radiation 2012 (UNSCEAR 2012) the definition of LDR is <0,1 mGy/min, while the threshold dose for defining LDR is <100 mGy, *Gray* being the measurement unit for the absorbed dose, calculated as the energy absorbed per unit mass within an object (2).

A number of non-cancer diseases have been reported in LDR-exposed populations, including atomic bomb survivors in Japan and liquidators of Chernobyl accident (3). However, these clinicalrisk is still largely undefined and there is great uncertainty regarding its relationship with low- and moderate-dose exposure.

In this paper, we reviewed the state of art about potential LDR-induced stochastic and deterministic damage, related genetic and biomolecular alterations, and possible measures to reduce LDR exposure. The radiation-induced susceptibility genes seems to be part of a larger biomolecular mechanism: a *Marples*' study identified the phenomenon of low-dose hyper-radiosensitivity, that is, cells die from excessive sensitivity to small single doses of ionizing radiation below 20-30 cGy.

It has been postulated that low-dose hyper-radiosensitivity is the default survival response of cells to radiation injury for doses less than 20-30 cGy. Low-dose hyper-radiosensitivity may be a consequence of radiation-damaged G2-phase cells entering mitosis with unrepaired DNA damage because X-ray doses <30 cGy fail to activate an ATM dependent 'early' G2 checkpoint: a considerable amount of work still needs to be

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conducted to completely answer the question (29).

Laboratory studies suggest that also processes other than the induction of specific locus mutations may be involved, such as increased transcription of specific genes, altered DNA methylation, delayed genomic instability (e.g. radiation-induced chromosomal alterations, changes in ploidy or mini- and microsatellite instabilities or other changes occurring long time after irradiation and manifest in the exposed cells progeny) (30).

We also briefly summarized the evidence of a causal association between moderate- and low-level radiation exposure and various types of non-malignant diseases, mainly focusing on three broad, clearly radiation-related conditions, including hereditary risks (so embryo-fetal abnormalities from radiation-induced germinal cell damage), cardiovascular disease and central nervous system effects. Furthermore, we discussed the need for a new molecular approach to study biological effects of radiation on cells, tissues and organisms, then better define health hazards of LDR.

Pregnant Exposure and Related Embryo-Fetal Damage

Due to the complexity of the issues surrounding fetal irradiation, there is no "standard" or predetermined advice that can be given to the expectant patient. However, it is possible to assist the patient in assessing the implications of the exposure if a systematic evaluation of the risk is performed. For this reason, we have summarized the state of the art about these implications.

Embryo/fetus is much more radiosensitive than neonatal and adult human being. The patterns of prenatal radiation-induced effects is not only dependent on radiation sources, radiation doses and dose rates, but also on the stages of fetal development (4).

Pregnant women, as all persons, are regularly exposed to radiation, such as naturally occurring environmental radiation and radiation from industrial, occupational, and medical sources. Internal exposure from radioactive materials inside the body (e.g., naturally occurring potassium 40 and carbon 14 from food, radon from water) is 11% of all common radiation exposure, while external exposure from environmental radioactive materials (e.g., natural gas, building materials, nuclear and coal power plants) is 15% of all common radiation sources. The risks of prenatal ionizing radiation exposure varies based on the embryonic/fetal stage of development. An embryo is most susceptible to radiation effects during the organogenesis phase (two to seven weeks after conception), as in the early fetal period (eight to 15 weeks after conception). The effects of exposure can be teratogenic, carcinogenic, or mutagenic ones and they are directly related to the level of radiation exposure. Non-cancer health effects are not observed when fetal radiation exposure occurs below a threshold dose of 0.05 Gy (5 rad) at any stage of gestation. In clinical practice, the threshold dose of the human embryo is probably closer to 0.10 to o.20 Gy (10 to 20 rad). After 16 weeks postconception, the threshold dose for noncancer effects increases to approximately 0.50 to 0.70 Gy (50 to 70 rad). During the preimplantation period (blastogenesis), radiation dose exposure greater than 0.1 Gy (10 rad) is associated with a risk of implant failure, representing an “all or none” phenomenon of early embryonic development. Mental retardation and growth restriction, including microcephaly, are the most common fetal malformations after significant radiation exposure during organogenesis and the early fetal period. Studies on Japanese atomic bomb survivors have shown that a threshold dose of 0.3 Gy (30 rad) at eight to 15 weeks after conception is associated with an increased risk of severe mental retardation (5). Mainly on the basis of animal studies and some observations following high-dose exposures in pregnant women, it is possible to consider that there is a threshold for these effects at about 0.1 Gy (6).

Heart and Vascular Disease

Data on high doses radiation-induced heart and coronary arteries disease are well established in literature, although only recent studies with high-quality individual dosimetry data allowed this risk to be estimated while adjusting for concomitant chemotherapy. An association between LDR exposures and late-occurring circulatory disease has only recently been suspected in the Japanese atomic bomb survivors and various occupationally exposed cohorts, instead, therefore it is still controversial. To note, excess relative risks per unit dose among the available moderate- and low-dose epidemiological studies are variable, however there were several difficulties undertaking this analysis, including: the high background occurrence of these type of disease in non-irradiated populations; making adequate allowance for factors other than radiation exposure (e.g. smoking, cholesterol levels, inherited predisposition); the lack of identified cellular mechanisms involved in their development (7). To set these standards, we have summarized the state of the art about potential acute and late effects on heart physiology from appropriate radiation exposure scenarios, including pertinent radiation types and dose rates.

We have reviewed the current literature about RRHD in early left breast cancer conserving therapy: indirect myocytes secondary effect caused by microvascular and macrovascular damage is the general mechanism. Accelerated atherosclerosis by radiation interacting with the pathological pathway of age-related coronary artery atherosclerosis, together with radiation reducing the heart’s tolerance to acute infarction as a result of microvascular damage, may reasonably increase morbidity and mortality from radiation-induced coronary artery disease (CAD) (8). In case of radiotherapy (RT) for breast cancer, so regarding high-dose heart exposure, it is well known that older radiation techniques are responsible for subsequent cardiac disease while modern radiation techniques presumably reduce the heart dose (current mean heart dose typically about 1 or 2 Gy for right breast irradiation, around 10 Gy for breast irradiation especially in women whose distance of heart from the thoracic wall is small and those requiring internal mammary irradiation. About this, Darby *et al.* recently reported heart ionizing radiation exposure during radiotherapy for breast cancer increases the rate of subsequent ischemic heart disease and the risk of a major coronary event linearly with the mean heart dose to the heart (9). A threshold dose of radiation to the heart below which there is no risk of damage still does not exist: during the last few years, several working group have produced evidence that radiation-related heart disease (RRHD)

might occur not only for doses >30 Gy but also for doses below, even if at the present time the role of radiation doses below 0.5 Gy in cardiac risk is unclear). Experimental animal models on median latency of heart failure by varying dose fractionations, revealed low-alpha/beta ratios (<4 Gy), suggesting a late-reacting-like behavior of the myocardium (10).

We also have to consider several risk factors potentially modifying cardiac risk, such as other organs irradiation (e.g. kidneys), kidney disease, hypertension, preexisting cardiovascular disease, diabetes, smoking, interactions with cardiotoxic drugs simultaneously used (anthracyclines, taxanes or trastuzumab). In fact, in atomic bomb survivors, radiation dose is also associated with increased hypertension incidence, suggesting that radiation dose may be associated with chronic renal failure (CRF), thus explaining part of the mechanism for increased CVD. Adams et al. found a significant quadratic dose relationship between radiation dose and possible chronic renal disease mortality that is similar in shape to that observed between radiation and incidence of hypertension in this population. These results suggest that renal dysfunction could be part of the mechanism causing increased CVD risk after whole-body irradiation, a hypothesis that deserves further study (11). It is true that the cohort of atomic bomb survivors has experienced difficult conditions as a consequence of war and atomic bombings, yet a recent Japanese update has revealed a significant dose-response relationship between radiation exposure and some hypertension-related, cardiovascular disease, and a non-linear correlation resulted for people exposed at younger age (12). Current knowledge refers to a 2003- study of 90000 US radiologic technologists found increase d risk of circulatory disease in those starting work before 1940 compared with those starting after 1960. Also atomic bomb survivors in the Hiroshima-Nagasaki Life Span Study (LSS) showed an increased risk by 14% per, with evidence of association between heart disease in this radiation exposed population and blood pressure alterations, inflammatory markers and lipid metabolism. Nowdays, survivors of radiation-treated breast cancer or Hodgkin Lymphoma (HL), and less frequently testicular cancer and peptic ulcer disease more commonly present with RRHD. Indeed there is evidence of a greater proportional increase in the cardiac death rate for childhood-irradiated HL than adults. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed 27% increasing mortality from heart disease for surgery-plus-RT-treated patients vs surgery alone, instead (with a 3% increasing death from heart disease per Gy), with an increasing trend in the left-sided vs right-sided radiation-induced cardiac mortality ratio as cardiac radiation doses for left-sided tumors irradiation are usually higher than those for right-sided ones, and despite breast irradiation implies lower cardiac radiation doses, thus smaller risk than HL (8;10). The estimates of population- based excess mortality risks for circulatory disease are similar to those for radiation-induced cancer, as also noted previously in relation to noncancer disease. If associations between low-level exposure to radiation and circulatory diseases reflect an underlying causal relationship that is linear at low doses, then the overall excess risk of mortality after exposure to low doses or low doses rates of radiation may be about twice that currently assumed based on estimated risks of mortality due to radiation-induced cancers alone (11). The PASSOS – Heart Study, a retrospective multicenter trial, concludes that contemporary RT techniques seems not to be associated with an increased risk of cardiac mortality or overall mortality for left-sided breast cancer relative to right-sided RT since they have reduced radiation exposure of the heart and CAD radiation dose but some exposure remains (13). Focusing on LDR exposure, recent data obtained from occupationally-exposed interventional cardiologists showed an increased carotid intima-media thickness and a decrease in telomere length in circulating leukocytes after 20- year exposure in the cardiac catheterization laboratory, compared to age-matched unexposed subjects (14). These subtle imaging and molecular alterations seems to be subclinical markers, intermediate end-points and long-term predictors of atherosclerotic disease, recent evidence over 22,000 exposed radiologic and nuclear medicine technicians confirmed increasing mortality not only for cancer but also for cardiovascular diseases (15;16). In the same way, an actual, international, multicentric study dealing with mortality from circulatory diseases among 308,297 nuclear workers in France, United Kingdom and United States (US) showed a statistically significant association between radiation dose and non-cancer causes of death, largely due to circulatory diseases (in particular cerebrovascular and ischemic heart accidents), although lifestyle factors as potential confounders among these estimates (17).

Brain Disorders

Another interesting topic about is radiation-induced brain disease: evidences indicate even LDR exposure leading to significant cognitive dysfunction because of radiation-induced inhibition of neurogenesis. Although the early clinical trials have had only modest success in modulating radiation-induced cognitive impairment, the future looks promising: we have summarized our knowledge of how radiation-induced brain injury develops, how it can be non-invasively detected, and how it can be treated, that has improved considerably over the past decade.

Recent studies reported cognitive impairment similar to that seen in the age-related one as effect of radiation exposure, that seems to be memory impairment as a consequence of radiation-induced inhibition of neurogenesis in the murine hippocampal dentate gyrus, because this neuronal changes resulted to be associated with an inhibition of long-term potentiation, an important type of synaptic plasticity. *Monje* and colleagues showed a single dose of 10 Gy to the rat brain completely abolishing the production of new neurons whereas surviving precursor cells adopt a glial phenotype (18) This dose is in the radiotherapy range, but a negative effect on neurogenesis has been clearly shown experimentally even in the low dose range, of interest for medical diagnostic and professional exposures. Another report provided evidence that the long-term (15 months) radiation injury is associated with irreversible damage to the neural stem cell compartment in the rodent and loss of oligodendrocytic precursor cells in both rodent and human brain. Manda *et al.* revealed changes with a substantial decline in the numbers of both the population of immature and proliferating neurons in the dentate gyrus (19).

Moreover, interesting aspects concerns radiation-induced cognitive impairments: genes associated with synapse and

neuron projections are enriched after low doses whereas ribosomes are enriched after both low and high doses, so synaptic signaling may be damaged after low-dose exposures. *Lowe* and colleagues indicated that the molecular response of the mouse brain within a few hours after low-dose irradiation is different from high-dose radiation exposure effects, involving the down-regulation of neural pathways associated with cognitive dysfunctions that are also down-regulated in a normal human aging and Alzheimer's disease, which high-dose exposures did not elicit: many of these low-dose down-regulated pathways are known to be associated with learning, memory and cognitive functions, and up-regulated genes were enriched in the pathways of oxidative phosphorylation, NRF2-mediated oxidative stress response, cell cycle checkpoint regulation, protein ubiquitination and amino acid metabolism, as well as the axon guidance signaling, actin cytoskeletal signaling, blood vessel formation pathway, cAMP signaling, insulin receptor signaling, even the integrin pathway required in memory networks (20).

In fact, despite Alzheimer's disease has been identified more than 100 years ago, its cause remains elusive. Although the chance of developing Alzheimer's disease increases with age, it is not a natural consequence of aging. Rodgers and colleague proposed dental X-rays to possibly damage microglia telomeres - the structures at the end of chromosomes responsible for how many times cells divide before dying and therefore their premature aging. Degenerated microglia lose their neuroprotective properties, resulting in the formation of neurofibrillary tau tangles and consequently, the neuronal death that causes Alzheimer's dementia (21).

As well palliative or prophylactic whole brain radiotherapy (WBRT) for intracranial metastases can bring harm subacute and late decline in memory and other cognitive functions, in particular when combined with systemic or intrathecal chemotherapy (22). To date, the real issue is to establish whether occupational low-to-moderate exposures, in the range of a cumulative dose over a professional lifetime of 1 to 4 Sv for interventional radiologists, cardiologists and electrophysiologists, may be associated with an increased risk for neurodegenerative diseases (23). It is now recognized that unprotected head is a target for radiation damage, and several reports have led to include brain cancer - especially on the more exposed left hemisphere - as a professional disease (24;25). The increased relative risk of a relatively rare disease such as brain cancer is of less concern than an increased relative risk of a relative common disease, such as Alzheimer's or Parkinson's or other neurodegenerative disorder, yielding greater absolute risks. Initial data obtained on professionally exposed interventional cardiologists show a 5-fold increased rate (compared to matched non exposed controls) of memory loss at neuropsychological testing, olphactory dysfunction or mood disorders. However, we need more data to assess whether low dose radiation can be considered an environmental toxicant accelerating brain aging in vulnerable subjects (26-28).

DISCUSSION AND CONCLUSION

Many difficulties are encountered in establishing specific LDR exposure-induced disease. The lack of specificity in clinical characteristics in this kind of disease; the long delay (years or decades) between LDR exposure and disease presentation; the high, spontaneous incidence of radiation-related diseases in general ageing population.

We reviewed the state of art about all these factors make and the causal relationship between chronic, LDR radiation exposure and possible clinical damage, because several, new trials are actually ongoing, but further studies are needed to better understand the real foundation of LDR-induc
ed disease, basing on this state of art.

The BEIR VII from the US National Research Council is actually the most comprehensive risk estimates of LDR-induced disease. This report states that man-made radiation exposure is quantitatively the most source of the whole radiation risks worldwide, other than the unavoidable natural background: medical exposure for radiological imaging represents about 79% of all the man-made radiation exposure in the US, while occupational exposures and nuclear power plants account for about 5% of it, and consumer products such as tobacco, the domestic water supply, building materials, televisions and computer screens are another great proportion, 16%. But yet, a comprehensive review of available biological and biophysical data from the Beir VII board is consistent with a linear dose-response relationship between LDR exposure and risk of human cancer, since low radiation beams deposit less energy within the irradiated cells so they may be considered less destructive per radiation track; likewise non-cancer and heritable health effects, which result noticeable after high-dose radiation exposure, may be smaller or at least more difficult to assess for LDR exposure (45). Although the vast amount of epidemiologic information allows reasonably precise estimates of radiation risks in general, estimating very LDR risks and related dose rates of interest for radiation protection remain uncertain. Better information on how radiation risk is modified by other types of exposure and host's affected characteristics is needed (44). It is also necessary to always justify the use of radionuclides and ionizing radiation in medicine, industry and research, taking the new epidemiological studies into account in optimization procedures for future use of them at the work place and in medicine. As Picano reported, the Euratom establishes that the need for an examination should be justified before a patient is referred to a radiologist or nuclear medicine physician and that a non-ionizing technique must be used whenever it will give grossly comparable information to a ionizing investigation. Three measures helping this process may be: firstly, a sort of radiological "driving license" so that inappropriate examinations could be avoided having penalty points for inappropriate prescriptions and the license with drawn if these infractions repeat; secondly, every scientific paper dealing with radiological testing should include a radiological table giving the cumulative radiological exposure for population in study; finally, patient should be required to sign an explicit and transparent informed consent form for each radiological exam: the form should spell out the type of examination, the exposure in effective dose (mSv), the dose equivalent in number of chest X-rays and the risks of fatal and non-fatal cancer and major genetic damage being transmitted to progeny: since doctors will have to inform patients, they will be informed by defalut about what they are proposing, and the consent form would also help reducing pressure from patients

for redundant examinations (36). On the other side, the American College of Radiology appropriateness criteria are an important tool for helping physicians to make the most appropriate imaging decisions for specific conditions, and widespread use of these criteria should reduce unnecessary CT scans. Mechanisms to evaluate appropriate dose levels, as well as guidance for reducing dosages, including reference levels for radiation dose are available, and participation in radiation dose registries can provide institutions with feedback on their radiation exposure levels in comparison with other institutions, even if further work is needed to investigate the balance of risks and benefits from CT scan use: if there is no difference in the expected benefit, the least invasive imaging tests (or those that do not require ionizing radiation) should be preferred, as well as increasing reliance on clinical history and physical examination should lead to avoiding children, pregnant women and obese patients exposure, only if necessary using laboratory tests and imaging to confirm the diagnosis or optimizing radiation dose with automatic tube current modulation (which modifies radiation dose depending on the thickness of the anatomic site to be examined), finally noise reduction filters (39;40).

Regarding regulation of medical radiation exposure, the International Atomic Energy Agency (IAEA) has produced an international consensus statement, the International Basic Safety Standards (BSS), but it has still not been adopted in some countries and only partially adopted in others. In addition, despite existing radiation protection programs, accidents, fatalities, and unwanted radiation exposures continue to occur, attributable to human error, computer program errors, equipment malfunction, disregard of existing policies and procedure (46;47). To date, the IAEA is also producing an "*educational reporting system for voluntary reporting of safety significant events in radiotherapy"* named Safety in Radiation Oncology (SAFRON), an ambitious project with the aim of developing and improving the safe planning and delivering of radiotherapy. Clinical audit may also contribute to protect patients in the clinical environment: according to the European directive 97/43/Euratom, clinical audits are defined as *"...a systematic examination or review of medical radiological procedures which seeks to improve the quality and outcome of patient care through structural review whereby radiological practices, procedures and results are examined against agreed standards for good medical radiological procedures, with modification of practices where indicated and the application of new standards if necessary..."* (42).

Since the diseases of interest can be relatively common and their impact may be influenced by factors other than radiation exposure, epidemiological observations are frequently unable to reveal clear evidence of radiation-related increased incidence at low-dose exposure. For this reason, recent advances in knowledge from experimental studies are very important to understand mechanistic basis of human disease. The development of newer medical technologies requires studies about children exposure to CT scan, and radiology technologists, radiologists and other physicians conducting interventional fluoroscopic procedures exposure. In conclusion, molecular studies can lead to a better knowledge of how genetic susceptibility might modify normal tissue radiation dose-response curve. Increasing evidences also suggest that genetic factors and other ones can affect the risk of disease: such factors will be better understood in the future.
Combining advances in imaging technology and greater awareness of radiation risk in medicine promoted by scientific professional societies is desirable (43).

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