Radiation Protection Dosimetry (year), Vol. 0, No. 0, pp. 0–0
DOI: 10.1093/rpd/nc0000

BIOLOGICAL EFFECTS OF LOW-DOSE RADIATION

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Received month date year, amended month date year, accepted month date year

The dramatic rise in diagnostic procedures, radioisotope's scans and intervention procedures has created a very valid concern for the long-term biological consequences from exposure to low doses of ionizing radiation (IR). Besides its unambiguous medical benefits, additional knowledge on the health outcomes is also essential. There has been growing scientific evidence in this regard in recent years. The aim of this review is to summarize the available information about the biological consequences of low-dose radiation (LDR) exposure in humans, based on studies. Most of the +studies in this review confirm the correlation between known biological risks and LDR (e.g., cytogenetical changes, cancer risk and radiation induced cataract). However, LDR studies still remain relatively new, despite the attention needed for the thorough exploration, and thus an encompassing view, of its biological effects and relevant mechanisms in the human body.

INTRODUCTION

The third millennium has seen the start of a new era in diagnostic imaging, in which the widespread use of computed tomography (CT) in clinical practice is nowadays essential. Undoubtedly, CT offers many diagnostic or screening benefits; however, its ubiquitous presence has caused the frequent exposure of the population to medical low-dose radiation (LDR)[(1,2)].

LDR is defined by radiation doses less than 100 mSv or a radiation exposure rate of 6 mSv or less per hour (<6 mSv/h)[(3,4)]. Contrary to high doses of irradiation, the biological effects of LDR exposure include linked bipolar effect phenomena, of which some could be labelled as positive (*i.e.,* radiation hormesis or hypersensitivity) and negative adaptive responses (*i.e.*, bystander effect, radioresistance, and genomic instability). These events suggest that the biologicals effect of LDR are very complex and still not fully understood.[(5)] Radiobiologists have been struggling to estimate the health risks of LDR in humans for decades. The high frequency of CT examinations, contrary to conventional radiography, is linked with the absorption of effective doses, *i.e.,* 15 – 30 mGy per single CT sequence, depending on the examined body parts, protocols and/or techniques. Moreover, the organs in the beam's pathway can receive doses as high as 10 – 100 mGy[(6)]. The absorption of these doses is significant, mainly in cases of repeated examinations when further health damage may be a direct result of radiation exposure during the CT. It is important to understand the possible risks of radiation in medical imaging so that the potential harm can be balanced against the potential benefit.

Our main interest in this review is to summarize the currently available knowledge concerning the biological risks related to CT scanning in patients. These risks have been arranged to provide an overview of LDR induced cytogenetical changes, cancer risk, and radiation induced cataracts.

METHODOLOGY

A scoping review approach was used in line with the Joanna Briggs Institute (JBI) and PRISMA Extension for Scoping Reviews (PRISMA-ScR) methodology [(7,8)]. The first step was to formulate a review question in PCC format (P= Population; C= Concept; C= Context): ***"What is the biological risk of low dose radiation from CT procedures in humans?"*** The question was formulated based on the authors' discussion and literature research. Only the studies focusing on biological effects or risks were included. The consulted studies had to include human patients or children, and no X-ray phantoms. We used various search term combinations, including:

- "Low dose radiation"; "low dose irradiation ", "low-dose ionizing radiation"
- "Computed tomography", "CT scanning", "CT screening", "whole body CT", "full body CT",
- "Cancer risk", "health risk"," biological effects"," biological risk", "adverse effects", "in vivo effect", "risk".

The PubMed, SCOPUS, and Medvik databases were used to search for publications. To provide a sufficient amount of material, articles were also searched manually in reference lists. Only the studies determining the biological effects or risks were included. A three-step search strategy was used, as recommended by JBI.

LDR-INDUCED BIOLOGICAL EFFECTS

DNA damage, chromosomal abnormalities, γ-H2AX

Background

Most of the established protocols in the assessment of radiation exposure are mainly based on radiation-induced DNA damage and disrepair, which can be detected by various cytogenetic assays including dicentric chromosomes assay (DCA), cytokinesis-block micronucleus (CBMN) assay, γ-H2AX assay, -omics technologies, and translocation analysis by fluorescence *in situ* hybridization (FISH) assay[9]. In general, all these cytogenetic assays are based on the frequency of chromosomal damage in peripheral blood cells, especially in lymphocytes[10]. This section of the review provides an overview of select studies focused on the effects of LDR generated by CT diagnosis through the analysis of DNA damage.

Multiple studies have evaluated the effects of LDR after CT scans based on the occurrence and frequency of micronuclei (MNs), dicentric chromosomes (DCs), or chromosomal translocation in peripheral blood cells. DCs are a byproduct of genome rearrangement placing two centromeres on the same chromosome[11]. Such chromosomal restructuring leads to aberrations, translocations or deletions[12]. Unlike DCs, micronuclei are whole, small nuclei found in the cytoplasm of mammalian cells. They can originate either by acentric fragments or whole chromosome loss at anaphase[13]. Radiation-induced MNs and DCs are mainly the result of unrepaired or misrepaired double-strand breaks[14]. Considering the characteristics and low frequency of induced MNs/DCs, one can predict the limitation of conventional DCs as a biological dosimeter for low-dose irradiation[14,15].

Overview

Kanagaraj et al.[16] investigated the effects of low dose X-irradiation in patients who underwent CT imaging. Their results showed significantly increased frequency of DCs and MNs after LDR exposure when compared to a previously unexposed status. The observed increment in chromosome aberrations indicate the trend of doses received in the patient's eyes, forehead and thyroid, confirming the effects of low dose radiation. The biological effects of low dose irradiation after a CT scan were also studied by Shi et al.[2], who examined DCs and ring chromosomes in peripheral blood lymphocytes using FISH assays. In said study, sixty patients with non-cancerous disease exposed to CT scans showed significantly increased frequency of dicentric and ring chromosomes with individual variation. These findings strongly suggest that the appropriate medical use of LDR should consider the individual differences in radiation sensitivity. Another report discusses the frequency of micronucleated reticulocytes (MN-RETs) in infants receiving CT scans, where the researchers confirmed its association with significant biological consequences in precursor erythrocytic cells in neonatal children with no prior CT scan history. In contrast, those infants with prior CT scans showed a significantly higher average in MN-RETs frequency when compared to the corresponding baseline values. These results confirm a significant cellular response increment after CT exposure in infants[17].

Geisel et al.[18] describe the relation between DNA double-strand breaks (DSBs) after cardiac CT scan and conventional coronary angiography (CCA). It was found that the correlation between the biological effects (DSBs) with the estimated radiation doses was excellent for CT; however, the relative biological effect of ionizing radiation from CCA was 1.9 times higher than the effective dose estimated by conversion factors. This suggests that the conversion factors may underestimate the relative biological effects of ionizing radiation from CCA.

Another study, by Lee et al.[19], focused on the analysis of chromosomal translocations through FISH assays, observing that the translocation frequency was significantly different between cases and controls, being more frequent in patients that had been repeatedly exposed to CT than in those patients who still had to undergo CT examination. A positive correlation between dose and response was found regarding translocation frequency and cumulative radiation exposure.

Virag et al.[20] and Kaatsch et al.[21] based their studies on a completely different principle to determine DNA damage induced by low dose radiation, *i.e.* by measuring the level of phosphorylated histone γH2AX and related changes in gene expression. In response to DNA damage after exposure to ionizing radiation, the histone molecule is phosphorylated on Ser139 to form γH2AX, whose level increases with the severity of the damage[22,23]. In general, protein modifications (γH2AX) and changes in gene expression are more sensitive than cytogenetic markers when estimating the risks of low-dose radiation exposure[24].

A study published in 2015 [25] evaluated the effects of X-rays after CT imaging in children, estimating the extent of DNA damage by scoring γ-H2AX foci in peripheral blood T lymphocytes. The study included 51 pediatric patients and, despite the low CT doses received, the study reports a median increment of 0.13 γ-H2AX foci/cell. Further, an increased frequency in DNA DSBs was observed for every patient, except for one chest CT patient that received a very low dose, *i.e.*, 0.14 mGy. The present study shows that nearly every CT procedure induces DNA DSBs in T lymphocytes of pediatric patients. Moreover, the results claim that the number of induced DSBs is strongly blood dose dependent.

In contrast to the γH2AX foci scoring method by fluorescent microscopy, Khan et al.[26] and Virag et

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al.[20] chose instead score these γH2AX foci through by flow cytometry[26], to assess immediate DNA damage after exposure to LDR. Significant gamma-H2AX positivity was found in cases versus control, with the most significant DNA damage found amongst cases with multiple CT scans, which causes more DSBs in comparison with a single scan. The widely used Cone-beam CT (CBCT) in dental practice could be harmful to undifferentiated cells such as dental pulp stem cells (DPSCs) since inaccurately repaired or unrepaired DSBs may lead to malignant transformation. The results of the study by Virag et al.[20] show that the level of H2AX phosphorylation in dental pulp cells increased significantly after 0.5 h of CBCT exposure, indicating transient DNA damage and a persistent inflammatory response in DPSCs, thus highlighting the potential risks of LDR exposure and the importance of dose monitoring in the pediatric population[20].

Another publication describes the induced changes in gene expression as a result of CT irradiation and demonstrated the utility of AEN, FDXR and DDB2 as low-dose RNA markers. In addition, the upregulation of DNA damage-related genes is reminiscent of the genotoxic nature of CT diagnostics, even at the low doses currently in use. This indicates that CT, even with the low doses applied currently, remains as a genotoxic stressor. The re-identification of three genes previously implicated in irradiation response underscores their usefulness as robust RNA markers for low-dose irradiation[21].

Radiation-induced cancer

Background

Carcinogenesis is considered to be the result of stochastic effects from radiation-induced DNA mutations and damage. The currently accepted, but intensively discussed, model of cancer caused by radiation exposure known as linear-no-threshold (LNT) model, is based on the presumption that any dose of radiation increases cancer risk and there is no such thing as a threshold level[27]. The first evidence regarding cancer induced by diagnostic X-rays and CT scans was reported by Berrington de Gonzalez[28] et al. and Brenner et al[29], respectively. Brenner's estimation of 1.5-2% chance of cancer induced by CT scans caused great controversy in scientific community. Even now, there are still two opposing opinions about the lifetime attributable risk (LAR) relative to CT scanning.

Undoubtedly, the biggest concern in radiation induced cancer is represented by the exposure of children, as they are up to ten times more radiosensitive and have a longer lifespan for radiation-induced cancer to develop[30]. The following section summarizes the current information concerning radiation induced leukemias and solid tumors in children, young adults, and adults.

Overview

Huang et al.[31] tried to estimate the radiation dose and cancer risk in adults, associated with retrospective and prospective electrocardiogram (ECG)-gated coronary CT angiography (CTA). A lifetime risk of cancer incidence of up to 0.37% (for 50-year-old patients) could be associated with retrospective ECG-gated coronary CTA. In contrast, prospective ECG-gated coronary CTA dramatically reduces the dose and cancer risk by 88%. De Jong et al.[32] investigated cancer mortality associated with repeated CT scanning of patients with cystic fibrosis (CF), whom underwent routine lifelong annual CT scans, finding that the cumulative risk of all cancer deaths was between 1-2 % by age 40. However, when CF survival increased to a median of 50 years, the combined cumulative mortality from hematologic and solid cancers was approximately 13% when annual CT scans were used from the age of 2 onwards. The risk decreased to approximately 7% when CT scans were discontinued at age 18. Burton et al.[33] evaluated the short-term risk of breast cancer after exposure to thoracic CT during maternal periods. They found 27 new cases of breast cancer following thoracic CT vs. 10,080 among the unexposed with an adjusted hazard ratio for breast cancer of 1.17.

Kritsaneepaiboon et al.[34] investigated young adult patients (age >15 years), who visited the emergency department with a traumatic injury and underwent one or more CT scans including at least two cancer sensitive tissue organs or areas (brain, neck, spine, chest, abdomen and pelvis). LAR declined with age and was higher in females, ranging from 0.008 to 1.18 % with mean and median of 0.14 and 0.08%, respectively. Another study done by Pearce et al.[35] examined patients with CT without previous cancer diagnoses younger than 22 years of age. During follow-up, 74 of 178,604 patients were diagnosed with leukemia and 135 of 176,587 patients were diagnosed with brain tumors. They noted a positive association between the dose from CT scans and leukemia, showing an excess relative risk [ERR] per mGy (0.036%), and brain tumors (0.023%). The risk of leukemia was positively associated with the estimated doses delivered by CT scans to the red bone marrow, as was also the risk of brain tumors associated with the estimated doses delivered by CT scans to the brain tissue. Berrington de Gonzalez et al. [36] collected and reviewed additional clinical information to assess whether the children had cancer-predisposing conditions or whether the CT scan may have been performed because of a preexisting or unreported cancer. They found cancer predisposing conditions in 4 out of 74 leukemia/myelodysplastic syndrome (MDS) cases and 13 out of 135 brain tumor cases. However, these conditions were unrelated to CT exposure. On the other hand, evidence of previous unreported cancer was found in 2 leukemia/MDS cases, 7 brain tumor cases, and 232 in non-cases related to increased number of CTs. The exclusion of these cancers reduced the ERR

per mGy by 15% from 0.036 to 0.033 for leukemia/MDS and by 30% from 0.023 to 0.016 for brain tumors.

Numerous studies were done to established this risk in children. Miglioretti et al.[37] confirmed that the risk of radiation-induced solid cancer is highest for abdomen/pelvis CT. In children younger than 5 years of age, leukemia risk was highest for head CTs (1.9:10,000), whereas that solid cancer risk for abdomen/pelvis CTs showed a greater risk (25.8-33.9:10,000 CT scans) in girls in comparison with boys (13.1-14.8:10,000 scans). Solid cancer risk was also high for chest and spine CTs in girls. The projected LAR of leukemia was highest for head CTs among children <10 years and decreased with age to 1.9:10,000 scans in children 10-14 years old. For these same children, the risk of leukemia was highest for abdomen/pelvis scans (1.0:10,000). A leukemia case was projected to result from 1 in 5,250 head scans performed in children younger 5 years old, contrary to 1 in 21,160 scans in children 10-14 years old. A study by Meulepas et al.[38] also evaluated leukemia and brain tumor risk following exposure to low-dose IR from CT scans in children younger than 18 years of age in a nationwide cohort. The mean cumulative bone marrow dose was of 9.5 mGy at the end of follow-up; however, leukemia risk was not associated with cumulative bone marrow dose. The cumulative brain dose was of 38.5 mGy on average and was significantly associated with the risk for malignant and nonmalignant brain tumors. This study confirmed increased brain tumor risk but no association with leukemia. Furthermore, Huang et al.[39] evaluated the possible association between pediatric CT examination and increased risk of brain tumor malignancies in exposed and non-exposed children cohorts (0-18 years of age). In the exposed cohort most children underwent head CT examinations at least once during the study period. The overall risk was not significantly different in the two cohorts. Although, the risk of brain tumor was significantly higher in the exposed cohort than in the unexposed one. The frequency of CT examination showed a strong correlation with the overall risk of malignant and benign brain tumors. Banerjee et al.[40] investigated children who underwent radiographic analysis due to trauma on the initial presentation, finding that no patient had significant head injuries detected with the CT scans. The mean LAR risk with CT scan in this group was 0.37%, finding a positive correlation between the radiation dose and increased cancer risk. One of the largest national studies was published by Mathews et al.[41] evaluating the cancer risk in children and adolescents following exposure to low dose IR from diagnostic CT scans. The data from 11 million cohorts revealed 60,674 new cases of cancer, including 3,150 out of 680,211 people exposed to a CT scan at least one year before cancer diagnosis. The mean duration of follow-up after exposure was of 9.5 years. The overall cancer incidence was 24% greater for exposed than for unexposed people, after accounting for age, sex, and date of birth. A dose-response relation was observed and the incidence rate ratio (IRR) increased by 0.16 (0.13 to 0.19) for each additional CT scan. The IRR was greater after exposure at younger ages (age groups: 1-4, 5-9, 10-14, and 15 or more years since first exposure) and increased significantly for many types of solid cancer (digestive organs, melanoma, soft tissue, female genital, urinary tract, brain, and thyroid); leukemia, myelodysplasia, and some other lymphoid cancers. There was an excess of 608 cancers in people exposed to CT scans (147 brain, 356 other solid, 48 leukemia or myelodysplasia, and 57 others lymphoid). The absolute excess incidence rate for all cancers combined was 9.38/100,000 person years at risk, with an average effective radiation dose per scan estimated in 4.5 mSv. This extensive study confirmed an increased incidence of cancer after CT scan exposure. Similarly, Nikita et al.[42] examined the magnitude of the risk of childhood leukemia after pediatric CT examinations using a nationwide case-control design. Also, this study confirmed that pediatric CT scans produce a small, but detectable increment in leukemia risk. Contrary to previous findings, White et al.[43] examined children who underwent cerebrospinal fluid shunt placement before 6 years of age, subsequent CT scanning and more than 10 years of follow-up. There were no cases of new benign or malignant brain, ocular, or thyroid tumors. There was no leukemia or any other tumors discovered in the follow-up period.

Radiation induced cataracts

Background

The eye lens is one of the most radiosensitive tissues in the body. Among the ocular structures, exposure of the lens to IR leads to the development of radiation induced cataracts (RIC), a tissue reaction clinically defined as progressive clouding of the lens, *i.e.* opaqueness leading to loss of vision[44]. Currently, the International Commission on Radiological Protection (ICRP) recommends the dose limit within a nominal threshold of 0.5 Gy to prevent RIC. In this regard, the equivalent dose limit for acute or protracted exposure and for occupational exposure of the lens of the eye has been established in 20 mSv/year[45].

The development of RIC results from genomic damage of lens epithelial cells (LECs). Cataractogenesis progressed due to downstream of LECs differentiation into lens fiber cells, the major component of the lens responsible for lens transparency and correct vision [46]. Due to significant radiosensitivity of lens, RIC has been intensively investigated by epidemiological studies to determine whether head CT scans significantly increase the risk of developing cataracts.

Overview

Recently, Weinstein at al.[47] reported an increased risk of cataracts associated with head (9.7%) and other CT

scans (6.6%), but not with neck CT. This study also showed that younger persons (<66 years of age) have a higher risk of RIC after head CT (1.61%); whereas that in persons older than 66 years, the CT-associated cataract risks were lower and similar for all CT procedures. On the contrary, The Blue Mountains Eye Study, another population study from performed in Australia, found no clear relation between the history of CT scans and the presence of cataracts [(48)].

A study by Yuan et al. confirmed that the patients evaluated under a CT scan have a significantly higher risk of RIC. However, radiation exposure from CT has only been associated with increased risk of cataracts (2.2%), which may become higher when CT exposure is more frequent, *i.e.*, five or more times (2.12%).

One of the most extensive studies in this regard was performed by Gaudreau et al. [(49)], who evaluated over 16 million individuals undergoing single/multiple CT scans across a 22-year period. This study estimated the risk of RIC between 3-8% after one to three CT scans. However, the lack of dose response in patients receiving four or more scans prevented an unequivocal confirmation that cataracts are correlated with head CT scan exposure.

CONCLUDING REMARKS

Most of the previously published radiation protection studies are based on the biological consequences of atomic bomb (A-bomb) or Chernobyl disaster survivors. Although these events are very different from the commonly received exposure from CT procedures, our results showed that even single CT scan induced numerous cytogenetical abnormalities, like DNA DSBs, chromosomal aberrations or γH2AX; with potential biological consequences that may affect an individual's mutation burden and enhance the risk of cancer.

The risk of radiation induced cataracts after diagnostic exposure to X-rays has been studied since 1993[(50)]. It is now known that the threshold for cataracts is lower than previously thought. Nevertheless, the conclusions made in recent studies differ on the effect that CT may have on the onset of RIC. Therefore, further research efforts with more precise study design and longer follow-up is needed.

In addition, intensive radiobiological research of LDR has shown many differences between already known mechanisms of high dose radiation. Many studies have already confirmed the beneficial biological effects of LDR on animal growth, development, health, and longevity, commonly termed as "radiation hormesis"[(51)]. A key to the improved understanding of LDR and the underlying biological mechanisms is still ongoing, trusting that it will solve the existing controversy.

Acknowledgement

The work was supported by the Ministry of Defence of the Czech Republic "Long Term Development Plan – Medical Aspects of Weapons of Mass Destruction" of the Faculty of Military Health Sciences Hradec Kralove, University of Defence, Czech Republic

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