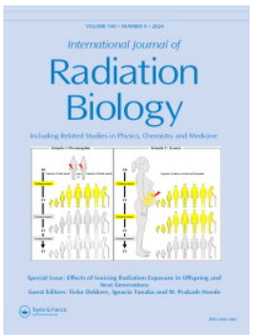

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REVIEW

Intergenerational effects of ionizing radiation: review of recent studies from human data (2018–2021)

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ABSTRACT

Purpose: The purpose of this paper was to conduct a review of the studies published between 2018 and 2022 to investigate radiation-related effects in the offspring of human individuals exposed to ionizing radiation.

Methods: The search identified 807 publications, from which 9 studies were selected for detailed analysis to examine for effects in children whose parents were exposed to various types and doses of radiation.

Results: The review does not yield substantial evidence supporting intergenerational effects of radiation exposure in humans. However, caution is required when interpreting the results due to limitations in the majority of the published articles.

Conclusion: This review, covering the period 2018–2022, serves as an extension of the previous systematic review conducted by Stephens et al. (2024), which encompassed the years 1988–2018. Together, these two papers offer a comprehensive overview of the available evidence regarding the intergenerational effects of parental pre-conceptional exposure to ionizing radiation. Overall, the findings do not provide strong evidence supporting a significant association between adverse (or other) outcomes in unexposed children and parental preconception radiation exposure.

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Transgenerational; intergenerational; hereditary; offspring; preconception exposure; ionizing radiation; health effect; epidemiology

Introduction

There is compelling evidence that radiation causes intergenerational effects in experimental animals (United Nations Scientific Committee on the Effects of Atomic Radiation 2001). Nevertheless, the detection of radiation effects in human germ cells and populations remains a challenging task. The Japanese A-bomb survivors constitute one of the largest irradiated human populations studied for effects in the next generations (Ozasa et al. 2019). However, up to now, no verifiable statistically significant increases in adverse health outcomes has been found in children whose parents had been exposed to ionizing radiation. The fundamental mechanisms underlying potentially radiation-related intergenerational effects remain poorly understood. The potential for radiation-related diseases is however a significant concern for the general public and a major issue for individuals exposed to radiation due to occupational, medical, or environmental sources.

A systematic review by Stephens et al. (2024) examined the evidence for effects in offspring of parental pre-conceptional exposure to radiation published between 1988 and 2018. The evidence for most adverse health outcomes was found to be inadequate meaning that formal determination of whether the health effect was (or not) associated with parental pre-conceptional radiation exposure was not possible. Heterogeneity between studies and in conclusions reached for individual studies were key factors in this (Stephens et al. 2024).

Since 2018, a number of studies have been published, contributing with more information to that reported in Stephens et al. (2024). The present paper aimed to review the studies on radiation-related effects in the offspring of human individuals exposed to ionizing radiation for the recent period of 2018 to 2022.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page et al. 2021) were used to provide guidance for this work aiming to answer the question: 'What is the effect of preconceptional exposure to ionizing radiation in offspring and next generations?' The protocol was recorded in the PROSPERO database (registration number: CRD42022312220).

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Data source and search

A literature search was conducted in October 2022 in PubMed. The queries were based on a combination of several keywords: 'transgenerational', 'hereditary', 'offspring', 'preconception', 'descendant', 'radiation', 'ionizing radiation', 'neutron', 'instability', 'health effect', 'genetic', 'genomic', 'epidemiology', 'nontargeted', 'congenital', 'stillbirth'. Inclusion of additional articles based on references from relevant publications or international reports was considered.

The selection process included the following steps: 1) title screening and selection from articles obtained through the queries; 2) abstract screening and selection from the previous screening; 3) full-text reading from the previous selection. The process aimed to be consistent with that used in a complementary review by Stephens et al. (2024).

Inclusion and exclusion criteria

Studies were eligible if their design was cohort, case-control, or cross-sectional, published in English between January 2018 and October 2022.

The studies were designed to assess genetic and non-genetic effects in the offspring of parents exposed to ionizing radiation before conception. A large number of outcomes were considered and investigated: chromosomal aberrations (or abnormalities), perinatal mortality (or stillbirths), major birth defects (or congenital abnormalities or malformations or abnormal development of the fetus), modification of the sex ratio, multifactorial diseases (metabolic diseases, cardiovascular diseases, high blood pressure, etc.), cancer, mortality from any cause, and lifespan.

Diverse situations of exposure to ionizing radiation were considered (environmental due to nuclear testing, nuclear warfare, accidents; occupational in nuclear workers, medical staff; medical in patients undergoing diagnostic exams, etc.).

Studies on offspring to the patients treated with radiotherapy before child's conception were excluded to avoid the bias of intergenerational effects that may be related to parental disease (mostly cancer) or potential concurrent chemotherapy, rather than to the radiation treatment. We also excluded studies where the exposure to ionizing radiation started before and continued after child's conception.

Conference abstracts, books, reports, reviews, meta-analyses, letters, and animal studies were excluded. However, the references of these excluded studies were examined to see if any studies could potentially meet the inclusion criteria of the present review. Some of the excluded articles are considered in the discussion section.

Results

Selection process

Figure 1 presents a flow diagram of the study selection process. The systematic search produced 807 records that were screened on title. 743 records were excluded after title screening because they were found to meet an exclusion criterion (post-conceptional exposure, books, conferences, animal studies, etc.). This led to the reading of 64 abstracts, from which 13 articles were identified for full text reading, finally selecting 8 studies suitable for inclusion in this systematic review work. Briefly, the reasons for exclusion during abstract screening were outcome or exposure outside the scope of the review (19 studies), study design not meeting inclusion criteria (33 studies), population with medical intervention for cancer (3 studies), and an overlap (one study) with the previous systematic review (Stephens et al. 2024). Moreover, 3 studies were excluded after reading the full text because they only addressed methodological aspects. One additional article was identified from bibliographic references of the retrieve articles, thus leading to 9 articles finally included in the systematic review.

Study characteristics

The characteristics of the 9 selected articles are detailed in Table 1. All the studies compared offspring of people who have been exposed to ionizing radiation before child's conception, with children of unexposed people. Some studies only look at exposures to ionizing radiation in fathers or in mothers, and some in both parents.

Sources of exposure to ionizing radiation include occupational (two studies), nuclear accidents (two studies), nuclear weapon tests (four studies on veterans or population), and atomic bomb exposure (one study).

As for the outcomes, four studies focused on *de novo* mutations (DNM), three studies on birth outcomes (low birth weight, congenital malformations, perinatal death, etc.), one study on the sex ratio in newborns, and one study on distress and general health of offspring to exposed parents.

The key findings of the nine included studies are summarized in Table 2.

1. Genetic studies

Holtgrewe et al. (2018) compared the occurrence of DNMs in the offspring of radar soldiers potentially exposed to high doses of ionizing radiation (N = 18) with that detected in offspring of unexposed parents (N = 28). The authors observed no significant difference in DNMs for single nucleotide variants (SNV), but they did observe an increased rate of multisite DNMs in the offspring of exposed fathers compared to the offspring of unexposed parents. Based on these results, the authors concluded that multisite DNMs might be suited for the assessment of DNA damage from ionizing radiation in humans, and they called for larger molecular epidemiologic studies (Holtgrewe et al. 2018). Nevertheless, due to the limited sample size and the absence of individual assessment of exposure before conception, the results of this study should be interpreted with caution.

Costa et al. analyzed the number of mutational events in the offspring of a population accidentally exposed to very low doses due to caesium-137 contamination after the radiological accident in Goiania (Brazil) in 1987. They compared

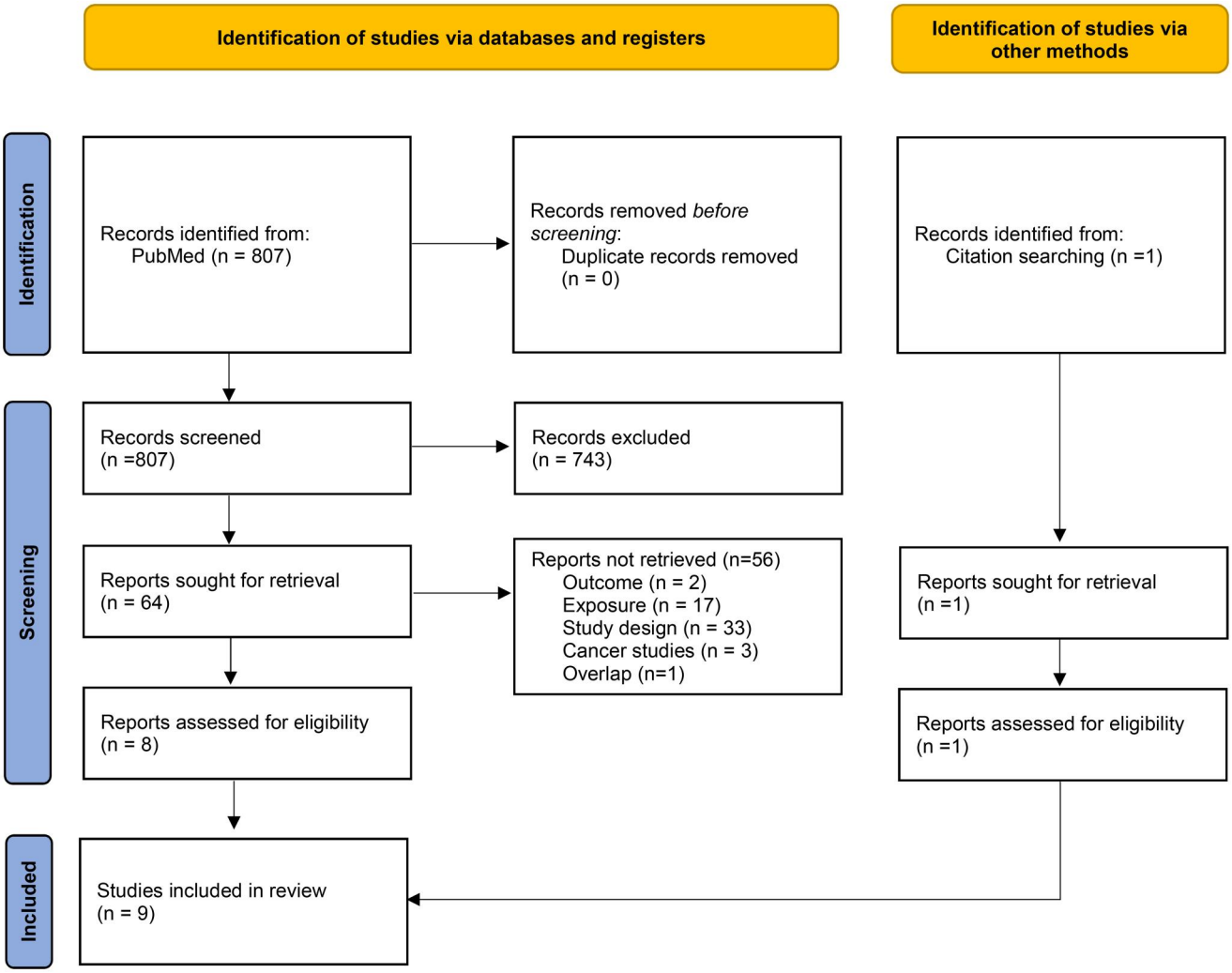

Figure 1. Flow diagram of the study selection process according to the PRISMA procedure.
PRISMA: preferred reporting items for systematic reviews and meta-analyses (see Page et al. 2021)

a group of children born to parents potentially exposed (N = 16) with a group of children born to unexposed parents from the same population (N = 8). The authors detected no significant difference between offspring of exposed and unexposed parents analyzing the number of mutational events. However, they did observe a significantly higher germline mutation rate of copy number variants across the whole genome in the offspring of exposed parents compared to offspring of non-exposed parents (Costa et al. 2018). Although the statistical analysis seems adequate and complete, the study has a small sample size, lacking individual assessment of parental gonadal exposure dose before conception.

Yeager et al. analyzed the total number of *DNMs* in children born from parents who were exposed as Chornobyl clean-up workers in Ukraine or evacuees from the settlements within the 70-km zone contaminated after the Chornobyl accident. They conducted a trio study of 130 children born to 105 mother-father pairs where one or both parents were exposed. The study strength is the well-designed protocol (Bazyka *et al.* 2020), and a reliable method for the estimation of cumulative gonadal preconception doses (Chumak *et al.* 2021), thus allowing dose-response analysis. Maternal and paternal gonadal doses were considered separately to account for any sex-dependent difference in intergenerational mutability. Yeager et al. found no evidence for a relationship between the total number of *DNMs* and preconception gonadal dose (Yeager et al. 2021). They also looked at the distribution and types of DNMs. The authors concluded that their results showed no evidence of a substantial effect of exposure to ionizing radiation on germline DNMs in humans, suggesting minimal impact on health of subsequent generations (Yeager et al. 2021). The study has many strengths, including large sample size, individual dose assessment and robust statistical analyses.

Moorhouse et al. analyzed genetic risks in a British nuclear test veteran family trio study. They analyzed the rate of DNMs in the offspring (N = 30) of military veterans present at the British nuclear tests in Australia and the South Pacific, compared to that in offspring of unexposed veterans group-matched on age, service and period of service in tropical regions (N = 30) (Moorhouse et al. 2022). Most of the test veterans have no recorded dose as they were not issued with film badges and no measurement for internal contamination took place. Accordingly, the authors allocated test

Table 1. Characteristics of the included studies.

First author, year	Country	Study design	Exposure situation	Study population	Exposure / Dose indicator	Outcome	Analysis methodology	Complementary information
Genetic studies								
Holtgrewe et al. 2018	Germany	Exposed/ unexposed	Occupational Chronic External	Offspring of radar soldiers (N = 18) with potential exposure to IR compared to offspring of unexposed parents (N = 28)	No individual dose assessment Local dose rate of 150 to 400 mSv/h	Mutation rate of *de novo* SNVs and multisite DNMs	Comparison of DNM rates Multiple linear regression adjusted for parents age	
Costa et al. 2018	Brazil	Exposed/ unexposed	Environmental Chronic External and internal	Children (N = 16) conceived after the Goiania accident by IR-exposed parents, compared to children from unexposed parents (N = 8)	No individual dose assessment Caesium-137 Estimates $\leq$ 0.2 Gy	Mutation rate of *de novo* CNV	Non-parametric Mann-Whitney U test to compare size and frequency of CNVs between exposed and non-exposed	Extensive review described in da Cruz et al. (1997) and dose estimates in IAEA report (2011)
Yeager et al. 2021	Ukraine	Trio	Occupational / Environmental Chronic External /internal	Children (N = 130) born to mother-father pairs (N = 105) enlisted as clean-up workers or evacuated after the Chornobyl accident	Paternal cumulative gonadal dose: mean 365 mGy, range 0–4,080 mGy; maternal dose: mean 19 mGy, range 0–550 mGy	Mutation rates of DNMs	Multiple regression adjusted for sequencing batch, maternal and paternal age, and maternal and paternal smoking status	Study design described in Bazyka et al. (2020); Dosimetric estimation described in Chumak et al. (2021)
Moorhouse et al. 2022	UK	Trio	Occupational Chronic External /internal	Families of British veterans of nuclear tests (N = 30) compared to families of British military personnel (N = 30) not present at nuclear tests	No individual dose assessment Only a subsample had a film badge: 84% were <10 mSv	Mutation rates of DNMs (SNV, Indels, SV, clustered)	Comparison between test veterans and control families Analysis using a 3-level proxy for IR exposure	Study design described in Rake et al. (2022)
Studies of pregnancy outcomes and birth events								
Nembhard et al. 2019	USA	Exposed/ unexposed	Environmental Chronic External and internal	Children of Marshallese mothers (N = 2488) compared to children born to non-Hispanic white mothers (N = 65,800)	No information on exposure status among the women	Rates of several birth defects from a statewide birth defects registry	Prevalence ratios from Poisson regressions adjusted for maternal age, education, marital status, and parity	
Andreassi et al. 2020	Italy	Exposed/ unexposed	Occupational Chronic External	Offspring of male catheterization lab workers (N = 193) compared to unexposed workers (N = 164)	No individual dose assessment Estimated total lifetime (30 years) occupational exposure: 0.5–1 Sv Considered occupational radiological risk scores	Low birth weight	Descriptive and comparison tests, Pearson correlations test, unconditional adjusted logistic regressions (age at conception, smoking habits, alcohol consumption)	
Yamada et al. 2021	Japan	Cohort	Environmental Acute External	A cohort of children of atomic bomb survivors (N = 71,603)	Gonadal dose estimates based on Dosimetry System 2002: mean dose of 0.02 and 0.03 Gy to paternal and maternal gonads, respectively	Major congenital malformations and perinatal death	Adjusted binomial regression models (maternal and paternal ages at birth, maternal parity, consanguinity, child's year of birth, child's sex, and city of registration)	Data description and previous analyses in (Neel and Schull 1956; Schull et al. 1981; Otake et al. 1990)
Hijikata et al. 2021	Japan	Exposed/ unexposed	Occupational Chronic External	Children of exposed (N = 57) and (N = 52) unexposed physicians	No individual dose assessment Estimates for unshielded surgeon: 0.15 mSv/ procedure, radiographer: 0.05 mSv/ procedure	Sex ratio	Fisher's exact test, multivariate logistic regression analysis (adjusted for paternal age at conception)	
Studies of other outcomes								
Dockerty et al. 2020	New Zealand	Descriptive study of exposed veterans and their offspring	Occupational External	New Zealand nuclear veterans (N = 83) with their offspring (N = 65)	No individual dose assessment	General health status, cancers, psychological conditions in veterans and offspring	Online survey of validated, self-reported questionnaire on health effects	

IR: ionizing radiation; DNM: *de novo* mutation; SNV: single nucleotide variant; CNV: copy number variant.

Table 2. Key findings of the included studies.

First author, year	Main results	Author's conclusion	Quality assessment of the strengths and limitations
Genetic studies			
Holtgrewe et al. 2018	• No significant difference in the number of DNMs for SNVs between exposed and unexposed • MSDN mutation rate per offspring higher in exposed (12/18) than non-exposed (5/28)	MSDNs are potentially useful tool for future assessment of DNA damage from IR in humans	- Small size pilot study - No individual dose estimates
Costa et al. 2018	• No difference in the number of mutational events - Higher germline CNVs mutation rate in children from exposed parents than unexposed	Low-dose IR exposure could be harmful by increasing the rate of *de novo* mutations in offspring	- Small study population - No dose assessment + Multiple comparison tests
Yeager et al. 2021	• Rate, class distribution, and SNV type distribution of DNMs in adult children born to parents exposed to IR are comparable to those reported in the general population. • No effect of radiation on the specific classes of DNMs (SNVs, indels, complex variants, or clusters)	No support for a intergenerational effect of IR on germline DNA in humans	+ Well-designed study protocol + Individual dose estimate + Adapted statistical analysis, and adjustment on parental age + Large sample size
Moorhouse et al. 2022	• No significant increase in the frequency of DNMs in the offspring to nuclear test veteran fathers	No evidence of increased mutations in the germline of a group of British nuclear test veterans.	- Lack of individual dose estimate - Small sample size + Adapted statistical analysis, and adjustment on confounding factors + Well-designed protocol
Studies of pregnancy outcomes and birth events			
Nembhard et al. 2019	• No difference in rate of total birth defects • Higher adjusted prevalence ratio of congenital cataracts (PR = 9.3; 95% CI: 3.1, 27.9), or common truncus (PR = 44.0; 95% CI: 2.2, 896.1) in children of Marshallese mothers compared to those of unexposed non-Hispanic white mothers	Estimates are unstable because of small sample size, so results are inconclusive.	- Small number of birth defect cases - No information on exposure status of mothers + Adapted statistical analyses, and adjustment for mother's age and ethnicity
Andreassi et al. 2020	• No significant difference in the prevalence of infertility and miscarriages, • Significant higher risk for low birth weight in the exposed workers (OR: 2.7; 95% CI: 1.1–6.3)	IR-exposure of males may increase low birth weight in offspring	- No dose assessment - Limited sample size - No maternal risk factors + Effort to consider exposure prior to conception + Adjusted regressions
Yamada et al. 2021	• Increased risk of perinatal death within 14 days in relation to the total parental gonadal dose (ERR/Gy = 0.21, 95% CI: 0.00,0.42) • Lack of statistically significant association between major malformations and paternal, maternal and total gonadal dose	Elevated risk of major malformation and perinatal death in relation to IR-exposure of parents, but most estimates were not statistically significant	+ Large sample size + Individual dose assessment + Preconception exposure + Dose-response calculation - Lack of information on lifestyle and socioeconomic factors among parents
Hijikata et al. 2021	• Low male sex ratio child in IR-exposed compared to unexposed workers (OR = 4.40 (95% CI: 1.60, 12.1) for having a female child).	Possible association between testicular radiation exposure and low male sex ratio in the offspring	- No available measurement for testicular radiation exposure - Small sample size + Consider exposure during the at-risk period + Adjustment for paternal age
Studies of other outcomes			
Dockerty et al. 2020	• Fertility, citing endometriosis, miscarriages and polycystic ovarian syndrome in 40% of offspring • Greater frequency of anxiety and depression in offspring compared to veterans	Higher distress and lower health status in Mururoa veterans and their offspring compared with normative values	- Self-reported information - Low response rate - Small sample size - No exposure information - No statistical test - No comparison with unexposed controls - Several biases

IR: ionizing radiation; DNM: *de novo* mutation; SNV: single nucleotide variant; CNV: copy number variant; MSDN: multisite *de novo* mutation.

veterans to a three-point exposure rank, based on their occupational history (for this, official records of their participation and particular roles were used together with information obtained from veterans who were on average aged 80 years old), and on environmental considerations at the test sites. The study protocol was detailed in Rake et al. (2022). Analyses considered total *de novo* SNVs, copy number variants, small insertion-deletions, structural variants, and clustered mutations. Overall, the authors found no evidence of increased mutations in the germline of British nuclear test veterans. They did, however, observe an elevated occurrence of single base substitution mutations within

mutation signature SBS16 in a subset of veteran's offspring, but concluded that this observation needs further investigation (Moorhouse et al. 2022). A major limitation of this study was the lack of dose information, and uncertainties in the exposure categories used in the analyses.

2. Studies of pregnancy outcomes and birth events

Large-scale nuclear weapons testing was conducted in the Marshall Islands between 1946 and 1958. To examine for any genetic consequences, Nembhard et al. evaluated birth defects in children of Marshallese mothers (N = 2488) compared with children born to non-Hispanic white mothers (N = 65,800). The authors found no significant difference in the total rates, but they did observe that infants from Marshallese mothers had higher rates of congenital cataracts (prevalence ratio [PR] = 9.3; 95% confidence interval [CI]: 3.1, 27.9) and of truncus arteriosus (PR = 44.0; 95% CI: 2.2, 896.1) than offspring to non-Hispanic white mothers (Nembhard et al. 2019). The study protocol was original but lacked exposure details. For instance, Marshallese mothers were considered as exposed individuals just by being born in the Marshall Islands at the time of testing, with no information on the duration of living on the islands.

Andreassi et al.(2020) analyzed the frequency of low birth weight in offspring of male workers in a cardiac catheterization laboratory (Cath lab) (N = 193) compared with children of unexposed workers (N = 164). The study included workers who had been employed in the Cath lab for >1 year at the time of conception of a child. The assessment of reproductive outcomes was done using a structured questionnaire. For the Cath lab male workers, the median gonadal dose (below the lead apron) may be of the order of 50 to 100 mSv for classical procedures, but it can be much higher for a complex interventional procedure. Over a professional lifetime of 30 years, the cumulative exposure can range from 0.5 to 1 Sv. Nevertheless, individual doses were not assessed in the study, but 'years of exposure at the time of conception' endpoint was used for the calculation of a radiological score. The authors mentioned that the estimated exposure by the surrogate of this score yields a reasonably good correlation. However, no difference in adverse reproductive events were found between higher and lower radiological scores. The authors also performed logistic regression analysis adjusted for smoking habits, alcohol, and age at conception to model the probability of adverse reproductive events occurrence. Results showed a higher prevalence of low birth weight in the offspring of the Cath lab workers than of the unexposed workers (Odds Ratio [OR] = 2.7; 95% CI: 1.1, 6.3). The authors concluded that chronic occupational radiation exposure of male workers is correlated with higher prevalence of low birth weight in their offspring (Andreassi et al. 2020). The authors also analyzed the copy number variation (CNV) in azoospermia factor region c (AZFc) of Y chromosome to characterize spermatogenic failure, making this marker non-relevant to the review's objective. The study was well designed, but the lack of individual dose assessment and absence of information on the mother's characteristics strongly limit the results interpretation.

Yamada et al. reanalyzed an earlier study of pregnancy outcomes among children born to atomic bomb survivors from Hiroshima and Nagasaki, Japan, using fully reconstructed data from the Atomic Bomb Casualty Commission (ABCC) genetic study on untoward pregnancy outcomes to include pregnancy terminations and congenital malformations that were excluded from previous analyses (Yamada et al. 2021). The re-analysis was based on refined estimates of parental gonadal dose based on Dosimetry System 2002 (Cullings et al. 2006) and improved analytical methods characterizing dose-response relationships. The ABCC genetic study was launched three years after the bombardments in 1948 and continued until 1954. It included the outcomes observed after the 20th week of pregnancy in 71,603 women from Hiroshima and Nagasaki. For each delivery, physicians and nurses had visited the baby's home to conduct a systematic examination and record all abnormalities, including minor defects. A positive dose-response relationship was shown for major malformations and perinatal deaths in relation to either the paternal dose (mean dose of 0.02 Gy), the maternal dose (mean dose of 0.03 Gy), or the joint dose of both parents (mean dose of 0.05 Gy). Nevertheless, statistical significance was only observed for the association between parental conjoint dose and perinatal deaths within ≤14 days (Excess Relative Risk per gray [ERR/Gy] = 0.21; 95% CI: 0.00, 0.42) (Yamada et al. 2021). The study strengths included accurate estimation of individual gonadal doses allowing assessment of dose-response relationships, considering maternal and/or paternal exposure to account for any sex-dependent difference in intergenerational mutability.

Hijikita et al. used logistic regression adjusted on paternal age at the child's conception to model the effects of the exposure variables (exposed/unexposed) on the probability of having a female child. They did show a statistically significant odds ratio for having a female child in physicians who worked in departments that used medical radiation and had a high possibility of testicular radiation exposure (N = 27) compared to physicians who worked in departments that did not use medical radiation (N = 52) (OR = 4.40; 95% CI: 1.60, 12.1). The authors tried to consider exposure up to 1 year before the birth of the child in order to localize the period at risk of changes leading to a potential decrease in the male sex ratio, but no dose assessment and no dose-response relationship have been provided. Nevertheless, physicians working in departments that used medical radiation but with a low possibility of testicular radiation exposure (N = 30) were also included, thus providing a gradient of exposure at the gonadal level. For this group of workers, the adjusted OR was not significant (OR = 1.03; 95% CI: 0.40, 2.61) compared to unexposed physicians (Hijikita et al. 2021). Despite a small sample size, this study is well conducted, and presents a low possibility of bias.

3. Studies of other outcomes

In New Zealand nuclear veterans (N = 83) and their offspring (N = 65), a higher distress and a lower health status have been mentioned in the Dockerty et al. study, as

compared with population normative values (Dockerty et al. 2020). However, this study was more descriptive than analytical, and did not provide information about statistical test comparison, nor on the level of exposure of fathers. In addition, and as mentioned by the authors, the inclusion of participants was on a voluntary basis, by accepting to answer an online questionnaire. The response rate to the study is extremely low and may suffer from a large selection bias (assuming that people in poor health would be more likely to respond).

Discussion

Contribution of recent results to our knowledge of intergenerational effects among humans

This review is an extension of the work done by Stephens et al. (2024), which included studies from 1988 to 2018. Following a similar methodology, nine studies addressing the potential effects of pre-conceptional exposure to ionizing radiation in humans were identified from 2018 to 2022 for inclusion in the present work. While the review by Stephens et al. (2024) showed that, despite the vast amount of research which has been published over many decades, the body of evidence remains inadequate to formally assess radiation-related adverse effects in the offspring of exposed parents. They concluded that if adverse health effects do occur in children of exposed parents, these effects are small and difficult to reproducibly measure.

In this companion review update, we analyzed the published evidence on the intergenerational effects of parental pre-conceptional exposure to ionizing radiation from papers published from 2018 to 2022. The literature search and selection led to only 9 studies. Among these, we can note the importance of genetic studies, especially the publication of two trio studies (Yeager et al. 2021; Moorhouse et al. 2022), which provide a new study design to analyze the genetic consequences of preconceptional exposures. The re-analysis of old data from the ABCC using updated dosimetric estimates and enhanced statistical methods is also notable, leading to a different interpretation of the association between parental dose and risk of perinatal deaths (Yamada et al. 2021). Overall, our review does not provide strong evidence for any intergenerational effects of radiation exposure in humans. The limitations of some of the published articles and the difficulties in studying intergenerational effects of radiation exposure in humans are discussed below.

Strengths and limitations of published studies

It is noteworthy that several study populations (medical workers, nuclear workers, residents, military veterans) with different exposures to ionizing radiation, as well as several health outcomes (birth defects, congenital diseases, cancers, biomarkers), were considered in both reviews, leading to large heterogeneities in the results. In addition, out of the nine studies selected in this review, most involved small sample sizes, leading to a weak statistical power, which is a limiting point in epidemiological studies. Moreover, as discussed in Stephens et al. (2024), there was no consensus in the statistical analyses or in the reporting of the studies' results, i.e. some provided relative risks, odds ratio, or only comparisons tests between exposed and non-exposed people.

Only two studies considered in this review did provide an estimate of the dose-response relationship, likely a consequence of the immense effort in gaining good dose estimates (Yamada et al. 2021; Yeager et al. 2021). An individual assessment of exposure is indeed a missing element in all other studies, which makes it impossible to provide in this present work a compilation of results in the form of a meta-analysis. Further work would be required to achieve this.

All these limitations hampered performing a qualitative assessment of the included studies using a validated scale. Only a relatively arbitrary assessment is provided in this review to inform readers about the lack of quality studies in this area. Similarly to Stephens et al. (2024), this work therefore highlights the need for good quality studies to answer questions about the suspected adverse intergenerational effects of ionizing radiation exposure in parents.

It is worth noting that all the studies included in this work have focused on exposure to ionizing radiation and its effects on the first generation of offspring only. However, adverse effects may manifest and persist for multiple generations driven by both genetic and epigenetic mechanisms, as proposed for other species (Xavier et al. 2019; Dubrova and Sarapultseva 2022). While to our knowledge no studies have been carried out on subsequent generations of humans, there seems to be a need for further work to address this issue, considering all the limitations we have mentioned above.

Also, many outcomes evaluated in this review for hereditary effects, such as birth defects or perinatal deaths, are not developed solely by genetic factors. It has to be kept in mind that such adverse effects may be confounded by many non-hereditary factors, such as lifestyle and socioeconomic status, that might be related to radiation exposure.

Summary of recent articles published in 2018-22 but not selected for the review

General syntheses

Boice J recently published an article about the likelihood of adverse pregnancy outcomes and genetic disease from exposure to radioactive fallout from the 1945 Trinity atomic bomb test in the United States. He presented an overview of human studies of the children of radiation-exposed parents, including studies of the offspring of environmentally exposed populations; childhood, adolescent, and young adult cancer survivors; atomic bomb survivors; and radiation-exposed workers. The studies sought to identify any excess of malformations, stillbirths, neonatal deaths, cancer, cytogenetic syndromes, single-gene disorders, or cytogenetic markers that would indicate an increase of hereditary genetic mutations in the exposed parents. The author concluded that '*the likelihood of discernible transgenerational effects is discounted because (1) in all large-scale comprehensive studies*

of exposed populations, no heritable genetic effects have been demonstrated in children of exposed parents; (2) the distribution of estimated doses from Trinity is much lower than in other studied populations where no transgenerational effects have been observed; and (3) there is no evidence of increased cancer rates among the scientific, military, and professional participants at the Trinity test and at other nuclear weapons tests who received much higher doses than New Mexico residents living downwind of the Trinity site'. (Boice 2020). It can be noted that the overview considered only articles published up to 2018, so before the period considered in our review.

A working group was set up in France by INSERM to assess the health consequences of nuclear testing in French Polynesia. This working group published a report in French in 2021, including in particular a review of knowledge on the intergenerational effects of exposure to ionizing radiation. The authors considered a large number of studies, including descendants of Hiroshima and Nagasaki bombing survivors, nuclear industry workers, and cancer survivors treated with radiotherapy, on various health effects, including birth defects and cancers. They concluded that the available studies on intergenerational effects in humans do not show any detectable effects for doses below a sievert, which drastically reduces the probability of transmission for doses in the mSv range, as is the case for fallout from nuclear testing in French Polynesia. However, they pointed out that these studies remain controversial and inconclusive because the doses are often much lower than those tested in animal studies, and the type of ionizing radiation and the mode of exposure are also very different. In addition, there is a lack of data in humans with appropriate follow-up of large cohorts over several generations. As a result of these methodological limitations, the possible intergenerational consequences of exposure to ionizing radiation in humans have not yet been confirmed (Inserm 2020).

Frangione et al. published a review of current knowledge about low-dose exposure to ionizing radiation and adverse birth outcomes in humans. The authors performed a systematic review and meta-analysis to synthesize the research of maternal and paternal exposure to low-dose radiation on low birth weight, miscarriage, pre-term delivery, and stillbirth. They included 26 studies published between 1990 and 2021, on populations exposed to occupational and medical sources of radiation, nuclear disasters, and those living near nuclear power plants. The authors concluded that their *'findings suggest that ionizing radiation increases the risk of adverse birth outcomes'* (Frangione et al. 2022). Nevertheless, their analysis did not separate exposure received before conception and after conception (n utero exposure), and only few of the studies considered prenatal exposure. Therefore, this review is not pertinent to assess the risk of preconceptional exposure.

Syntheses of health effects among offspring of A-bomb survivors

Ozasa et al. published a review of the epidemiological studies of people who were exposed to atomic bomb radiation and their children who were conceived after parental exposure to investigate the late health effects of atomic bomb radiation and its intergenerational effects. Those studies included cohorts of the atomic bomb survivors (the Life Span Study: LSS), n utero survivors, and the children of the survivors. The authors concluded that no increased risks due to parental exposure to radiation have been observed for malignancies or other diseases in the children, but further investigations are required (Ozasa et al. 2019).

Jordan reviewed the long-term epidemiological studies of the irradiated survivors and their offspring after the atomic bombing of Hiroshima and Nagasaki. In studies on the offspring of these survivors, no statistically significant deleterious effect on malformation frequency, incidence of mutations or mortality from cancer and other diseases has been seen so far. These data show that health risks from radiation are limited, but they are not applicable to complex situations such as nuclear power station accidents that involve diverse types of radiation as well as contamination by radioactive materials (Jordan 2018).

Review of genetic or health effects among offspring of cancer patients

Boice published a review on human studies of the children of radiation-exposed parents, which also included studies evaluating the offspring of childhood, adolescent, and young adult cancer survivors treated with radiation. Based on results published before 2019, the evaluation over 35,800 children of 21,205 cancer survivors treated with radiation therapy showed no evidence of intergenerational effects. While some studies have identified adverse pregnancy outcomes, these effects were attributed to somatic rather than hereditary factors (Boice 2020).

Al-Jebari et.al 2019 published a nationwide register study to investigate whether anti-neoplastic treatment for testicular germ-cell cancer implies additional risk of congenital malformations. The study included 2380 fathers with testicular cancer and their 4207 children, comparing the children conceived after the father received cancer treatment to the children born before treatment. The authors concluded that children fathered by men with testicular germ-cell cancer had a higher risk of congenital malformations, but the risk was not associated with radio- or chemotherapy. In addition, this increase of the risk was very small and related to rare conditions (Al-Jebari et.al 2019).

Meistrich published a review to update the data on genetic and epigenetic effects of genotoxic agents on animal and human spermatozoa exposed during spermatogenic development and developed a scheme that can be used to estimate the risks of genetic damage to offspring. The author concluded that the risk of mutations in spermatozoa varies with the type of cytotoxic agent and the time of exposure during the therapy. However, further studies are needed to improve the accuracy of the estimates and to provide more comprehensive guidelines on the risk of different doses of cytotoxic agents (Meistrich 2020).

Nielsen et.al (2018) published a review to examine whether cancer survivors diagnosed before age 35 years were

more likely to have offspring with chromosomal abnormalities than their siblings. The study included 14611 offspring (14580 live-born children and 31 fetuses) of 8945 Danish cancer survivors and 40859 offspring (40794 live-born children and 65 fetuses) of 19 536 siblings. The authors concluded that the cancer survivors can have children without fear of transmitting genetic or chromosomal abnormalities related to their cancer or treatment (Nielsen et al. 2018).

Perspectives for further analyses on intergenerational effects among humans

The re-appraisal of earlier A-bomb data concluded that parental exposure to radiation is (mostly non-significantly) associated with increased risks of major congenital malformations and perinatal death (Yamada et al. 2021). As highlighted in the present review and discussed in Stephens et al. (2024), these new results need further consideration into the evidence surrounding congenital abnormalities. The potential to undertake a new pooled analysis of eligible studies from Stephens et al. (2024) with information from Yamada et al. (2021) on congenital abnormalities should be explored.

Conduction of trio studies appears today as a promising way to improve the analysis of genetic effects of preconceptional radiation exposure. Nevertheless, an effort to homogenize protocols, and especially studied outcomes would be worth to improve interpretation and comparability of results. In the study of Moorhouse et al. (2022), the authors observed an elevated occurrence of single base substitution mutations within mutation signature SBS16, noting that further investigations may be worthwhile to determine the potential relevance of this observation. Future potential for genomic studies should be explored therefore which examine the spectrum of genomic mutations further to understand the importance, if any, of different types or patterns of mutation (rather than just mutational load).

One major limitation is that published studies considers only one generation. It is interesting to note that Moon et.al published an ongoing cohort study protocol on the health status of Korean Atomic Bomb survivors and their offspring. For this, the authors are planning to recruit 1500 atomic bomb survivors and their offspring by 2024, including descendants from the first, second and third generation. For 200 trios it is planned to identify DNMs using whole genome sequencing to compare with DNM prevalence in general population (Moon et al. 2023).

Studies of genetic or health effects among offspring of cancer patients were excluded from our review and from that of Stephens et al. (2024). An update of the literature review on that topic could be a useful complement to the present paper.

Finally, and similar to the review performed by Stephens et al. (2024), it appears that the interpretation of our review of the literature is hampered by the strong limitations of some of the published articles. A major route of improvement for the future is toward the improvement of the studies quality, and homogenization of study protocols.

Potential impact on radiological protection

Hereditary effects are included in the system of radiological protection since 1956 (International Commission on Radiological Protection 1956). But this topic has not been updated since 2001 by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (UNSCEAR 2001) and since 2007 by the International Commission on Radiological Protection (ICRP) (ICRP 2007). The possibility of radiation-related deleterious effects in offspring is still today a major source of fear for the general public and a major concern for parents exposed to ionizing radiation from occupational, medical or environmental sources.

The ICRP considers that a revised assessment of the harmful effects of ionizing radiation in offspring and next generations is needed to inform future global revisions of the system of radiological protection. A Task Group on this topic was launched in 2022 (https://www.icrp.org/icrp_group.asp?id=189).

The first task to support this revision of the consideration of hereditary effects in the system of radiological protection is to perform a review of available results in the scientific literature. The present paper, and several others published in this issue of the International Journal of Radiation Biology, will contribute to this revision process.

Conclusion

This review on the period 2018-2022 is an extension of the literature review performed by Stephens et al. (2024) which covered the 1988-2018 period. Together, these two papers provide a comprehensive overview of the available epidemiological evidence on the intergenerational effects of parental pre-conceptional exposure to ionizing radiation. Overall, the results do not provide strong evidence for an association between adverse effects in unexposed children and parental preconception radiation exposure, but interpretation of the results is hampered by limitations associated with some of the published papers.

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