Literature Review on the Health Impacts of Exposure to Ionising Radiation

24 February 2023

ALLEN + CLARKE CONSULTING

Document status:	Report finalisation
Version and date:	v2.0 24 February 2023
Author(s):	Carolyn Hooper, Kelsey Morrison, Robbie Manning, Elizabeth Bohm
Filing Location:	NZ-Work/Veterans Health Advisory Panel/2022 Lit review health impacts of exposure to nuclear radiation/04 Deliverables/Reports/Report finalisation
Peer / technical review:	Anna Gribble, Gabrielle Jenkin
Verification QA changes made:	Carolyn Hooper, Kelsey Morrison
Proofread:	Sean Stack, Kelsey Morrison
Formatting:	Kelsey Morrison
Final QA check & approved release:	Gabrielle, Practice Manager – Evaluation and Research

ALLEN + CLARKE

+64 4 890 7300
office@allenandclarke.co.nz
www.allenandclarke.co.nz

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABCC	Atomic Bomb Casualty Commission
ADBI	Atomic Bomb Disease Institute of the Nagasaki University Graduate School of Biomedical Sciences
AHS	Adult Health Study
AML	Acute Myeloid Leukaemia
ARS	Acute Radiation Sickness. Systemic disease due to momentary (or short-term) whole-body exposure to ionising radiation at a dose more than 1 Gy.
ChNPP	Chernobyl Nuclear Power Plant
CI	Confidence intervals
CLL	Chronic Lymphocytic Leukaemia. It is not clear what causes CLL, but it is not proven to be associated with radiation exposure. Thus, in the articles reviewed relating to leukaemia, it is routinely a noted (by the article authors) to be excluded.
De novo variants	Mutation/alteration in the genome of any organism that was not present or transmitted by their parents.
Dose of ionising radiation exposure	Low-, moderate-, and high-dose ionising radiation exposure are terms often discussed in the literature. Generally accepted bands were proposed by the United Nations Scientific Committee on the Effects of Atomic Radiation (2012) and are as follows (as cited in Ruhm et al., 2022): • Low-dose, between 10 mGy and 100 mGy • Moderate-dose, between 100 mGy and 1000 mGy (or 1 Gy)
Dose-response	A mathematical model that explains whether the level of response increases or decreases with dose, and how rapidly the response changes as a function of dose. A linear dose-response refers to a relationship between dose and response that is a straight line. This means that the rate of change is the same at any dose.
DREF	Dose Rate Effectiveness Factor
EEG	Electroencephalogram. A method of recording electrical brain activity.
ERR	Excess Relative Risk. The rate of disease in an exposed population divided by the rate of disease in an unexposed population (or relative risk), minus 1.0. An ERR of 0.5 means a 50 percent increase in risk or rate over the risk or rate experienced by the general population. Often expressed as ERR per unit of exposure such as Gy or Sv.
Gy	Gray. A unit of absorbed radiation equal to the dose of one joule of energy absorbed per kilogram of matter, or 100 rad.
Hypocentre	Location on the ground, directly below an atomic bomb.
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IED	Intermittent Explosive Disorder

Abbreviation	Definition
IHD	Ischemic Heart Disease
IR	Ionising Radiation
INWORKS	International Nuclear Workers Study
LANL	Los Alamos National Laboratory, New Mexico, United States
Low-LET	Low Linear Energy Transfer
LSS	Japanese Life Span Study
MDS	Myelodysplastic Syndromes. A group of disorders where the production of normal blood cells in the bone marrow is adversely affected leading to the production of poorly functioning blood cells.
MGUS	Monoclonal Gammopathy of Undetermined Significance. A premalignant state, to malignant states such as multiple myeloma, macroglobulinemia, malignant lymphoma, and amyloidosis.
Morbidity	The state of having a specific disease. Often expressed as incidence or prevalence. Incidence refers to the occurrence of new cases of a disease within a population over a specified period of time. Prevalence refers to the proportion of a population that has a specific disease, and includes both new and existing cases.
Mortality	The number of deaths that occur in a population. Often expressed as a rate, calculated by dividing the number of deaths that occur due to a specific disease by the total population.
MPS	Million Person Study
mGy	Milligray. A unit of absorbed radiation equal to one thousandth of Gy, or 0.1 rad.
Non-solid cancer	Liquid tumours that circulate in the bloodstream around the body, and include types of leukaemia, lymphoma, and myeloma. In this context CLL is excluded.
NHL	Non-Hodgkin's Lymphoma
NPP	Nuclear Power Plant
OR	Odds Ratio. The ratio of the likelihood of an event's occurrence to the likelihood of its non-occurrence. An odds ratio of 1.00 indicates the risk is comparable in the two groups, an odds ratio greater than 1.00 indicates increased risk, and an odds ratio lower than 1.00 indicates decreased risk.
PCL	A posttraumatic stress disorder checklist
qEEG	Quantitative Encephalogram, see also EEG
RERF	Radiation Effects Research Foundation, formerly known as ABCC
RR	Relative Risk. The rate of disease in an exposed population divided by the rate of disease in an unexposed population. For example, 75 deaths per 100,000 exposed population per year, divided by 25 deaths per 100,000 unexposed population per year, equals a relative risk of 3.0. A relative risk of 1.00 indicates the risk is comparable in the two groups, a relative risk greater than 1.00 indicates increased risk, and a relative risk lower than 1.00 indicates decreased risk. For example a relative risk of 0.7 indicates that the risk is reduced by 70%.
SO	Shelter Object

Abbreviation	Definition
Solid cancer	Organ tumours that form one or multiple masses in organ systems and can occur anywhere in the body. Does not contain liquid or cysts.
SMR	Standardised Mortality Ratio. Ratio of the number of deaths observed in a population over a given period to the number that would be expected over the same period. An SMR greater than 1 indicates that the number of observed deaths was greater than the number of expected deaths. An SMR equal to 1 indicates that the number of observed deaths was equal to the number of expected deaths. An SMR lower than 1 indicates that the number of observed deaths was less than the number of expected deaths.
SNV	A DNA sequence variation that occurs when a single nucleotide (adenine, thymine, cytosine, or guanine) in the genome sequence is altered.
Sv	Sievert. A measure of the stochastic health risk of ionising radiation. The International Commission on Radiological Protection considers that one Sv results in a 5.5 percent probability of eventually developing fatal cancer, however this is based on the disputed linear non-threshold model of ionising radiation exposure.
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
USAAF	United States Army Air Forces
WHO	World Health Organization

Spelling conventions

New Zealand spelling conventions have been used in this review, with the exception that direct quotations and article titles use the spelling conventions of the publication. This is particularly evident with the words ‘ionising/ionizing’; ‘leukaemia/leukemia’; and ‘oesophagus/esophagus’.

Ionising radiation definitions and terms

Ionising radiation

The International Commission on Radiological Protection (ICRP) defines radiation as “energy, in the form of waves or particles, moving through space”.[1] The ICRP defines ionising radiation as “radiation with enough energy to break chemical bonds”.[2] Common types of ionising radiation include X rays, gamma (photon) radiation, alpha radiation, beta (electron) radiation, and neutron radiation.

Radiation dose

Radiological protection considers that there are three measurements of the amount ionising radiation exposure, or ionising radiation dose.[3] These are outlined below in table 1. Whilst

[1] http://icrpaedia.org/ICRP%C3%A6dia_Guide_to_the_Basics_of_Ionising_Radiation
[2] Ibid
[3] http://icrpaedia.org/Absorbed,_Equivalent,_and_Effective_Dose

absorbed dose is the only type that is a measurable, physical quantity, it is effective dose that is most frequently used.[4]

Table 1. Characteristics of three types of radiation dose[5]

Absorbed dose	Equivalent dose	Effective dose
Amount of energy deposited by radiation in a mass. The mass can be anything, for instance a person, air, or water.	Calculated for individual organs.	Calculated for the whole body. Reflects the overall risk. Most frequently used.
Measurable, physical quantity.	Based on the absorbed dose to an organ, adjusted for the effectiveness of the type of radiation.	Addition of equivalent doses to all organs, each adjusted for the sensitivity of the organ to radiation.
1 gray = 1 joule of energy deposited in 1 kilogram of material (1 Gy = 1 J/Kg)	Absorbed dose multiplied by the appropriate radiation weighting factor.	Equivalent dose to the organ multiplied by the appropriate tissue weighting factor, then all organs summed.
Grays (Gy) or milligrays (mGy) mGy is 1/1000th of a Gy	Sieverts (Sv) or millisieverts (mSv) to an organ mSv is 1/1000th of a Sv	Sieverts (Sv) or millisieverts (mSv) mSv is 1/1000th of a Sv
Rad (USA) 1 rad = 0.01 Gy	Roentgen equivalent man (rem) or millirem (mrem) (USA) mrem is 1/1000th of a rem 1 rem = 0.01 Sv	Roentgen equivalent man (rem) or millirem (mrem) (USA) mrem is 1/1000th of a rem 1 rem = 0.01 Sv

Equivalent dose is calculated using radiation weighting factors. These numerical values depend on the type and energy of radiation causing the dose, and are depicted in Table 2 below.[6]

For example, gamma (photon) radiation with a radiation weighting factor of 1, and an absorbed dose of 10 mGy in an organ results in an equivalent dose of 10 mSv to the organ. Similarly, alpha radiation with a radiation weighting factor of 20, and an absorbed dose of 10 mGy in an organ results in an equivalent dose of 200 mSv to the organ.

Effective dose is calculated similarly with the use of tissue weighting factors. The equivalent dose for each organ is multiplied by the appropriate tissue weighting factor and then all equivalent doses are summed.

[4] Ibid
[5] Adapted from http://icrpaedia.org/Absorbed,_Equivalent,_and_Effective_Dose
[6] https://www.euronuclear.org/glossary/radiation-weighting-factors/

Table 2. Radiation weighting factors by radiation type and energy[7]

Radiation type and energy	Radiation weighting factor
Photons, all energies	1
Electrons, myons, all energies	1
Neutrons < 10 keV 10 keV to 100 keV > 100 keV to 2 meV > 2 MeV to 20 MeV > 20 MeV	 5 10 20 10 5
Protons > 2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

Exposure effects

Radiological protection groups the harmful effects of exposure to ionising radiation into two categories: deterministic effects and stochastic effects. Stochastic effects are of greatest relevance for this review. The key characteristics of deterministic and stochastic effects are summarised in Table 3 below.

Table 3. Characteristics of deterministic and stochastic effects[8]

Deterministic effects	Stochastic effects
Only appear at relatively high doses. Includes skin burns and damage to the lens of the eye. Also known as harmful tissue reactions.	Assumed to pose some risk even at low doses. Includes cancer and heritable effects.
Do not appear below a dose threshold. And above the dose threshold, the higher the dose the most severe the effect.	Evidence that doses above 100 mSv can increase the risk of cancer. Evidence for doses below 100 mSv is less clear. For radiological protection purposes it is assumed that even small doses might result in small increased risk.

[7] Taken from https://www.euronuclear.org/glossary/radiation-weighting-factors/
[8] Adapted from http://icrpaedia.org/Effects_of_Exposure

Deterministic effects	Stochastic effects
No deterministic effects expected below an absorbed dose of 100 mGy (above natural background exposure), and thresholds for most effects are much higher.	An extra effective dose of 200 mSv (above natural background exposure) increases the risk of fatal cancer from the typical worldwide average of about 25% to 26%.
Rare, although can occur as a result of sophisticated medical procedures, or accidents. In severe accidents, very high doses received in a very short time can lead to acute radiation syndrome or even death.	Although genetic effects have been seen in animals, none have ever been seen in humans. Even so, for radiological protection purposes, a small risk of heritable effects is assumed.

In summary, deterministic effects require a dose threshold to be met for damage to become clinically observable, whereas stochastic effects do not have a dose threshold (Kamiya et al., 2015). The severity of deterministic effects depends on the absorbed dose, dose rate, and radiation quality, whereas the probability of the occurrence of stochastic effects (not severity) depends on the dose (Kamiya et al., 2015).

Natural background radiation exposure

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reports that the "estimated value of worldwide average annual exposure to natural radiation sources remains at 2.4 mSv…and most annual exposures would be expected to fall in the range 1-13 mSv".[9] This figure includes:

- 0.39 mSv from cosmic radiation (range 0.3-1.0 mSv) e.g. from the sun
- 0.48 mSv from external terrestrial radiation (range 0.3-1.0 mSv) e.g. from the soil
- 1.26 mSv from inhalation (range 0.2-10 mSv) e.g. from the air
- 0.29 mSv from ingestion (range 0.2-1.0 mSv) e.g. from food and water.[10]

Medical test related radiation exposure

Average doses from common medical imaging tests include:[11]

- 0.1 mSv from a single chest x-ray, equivalent to about 10 days of natural background radiation
- 0.4 mSv from a mammogram, equivalent to about 7 weeks of natural background radiation

[9] https://www.unscear.org/unscear/uploads/documents/publications/UNSCEAR_2008_Annex-B-CORR2.pdf
[10] Ibid
[11] https://www.cancer.org/treatment/understanding-your-diagnosis/tests/understanding-radiation-risk-from-imaging-tests.html#:~:text=A%20single%20chest%20x%2Dray,background%20exposure%20over%207%20weeks

- 8 mSv from a lower gastrointestinal series using x-rays of the large intestine, equivalent to about 3 years of natural background radiation
- 10 mSv from a computed tomography (CT) scan of the abdomen and pelvis
- 25 mSv from a positron emission tomography/computed tomography (PET/CT) scan for cancer.

Dose limits

The ICRP recommends dose limits for public and occupational exposure in order to restrict harmful exposure to radiation. Dose limits are applied to radiation received beyond natural background radiation. Public exposure is that sustained by members of the public (excludes occupational and medical exposures), for example visiting a hospital, living near a nuclear power plant, and radon gas in the home.[12] Occupational exposure is that sustained by workers in the course of their work, for example working in a hospital or nuclear power plant.[13] The ICRP outlines dose limits for both effective dose and equivalent doses for the lens of the eye, skin, and hands and feet. The effective dose limits are included below.

- The effective dose limit for public exposure is “1 mSv in one year. In special circumstances, a higher value could be allowed in a single year, provided that the average over five years does not exceed 1 mSv per year”.[14]
- The effective dose limit for occupational exposure is “20 mSv per year, averaged over defined periods of five years, with no single year exceeding 50 mSv. After a worker declares a pregnancy the dose to the embryo/foetus should not exceed about 1 mSv during the remainder of the pregnancy”.[15]

12 http://icrpaedia.org/Exposure_Categories_and_Situations
13 Ibid
14 http://icrpaedia.org/Dose_limits
15 Ibid

EXECUTIVE SUMMARY

This review of published literature explores the physical and psychological health impacts of ionising radiation on humans and their descendants. The most recent, high-quality evidence was reviewed and summarised.

Non-solid cancers. Findings for non-solid cancers vary by cohort characteristics and the multiple types of disease. There appears to be more and stronger evidence of an association between exposure to ionising radiation and leukaemia, lymphoma, and multiple myeloma than for other non-solid disease conditions. This review found associations in relation to Hiroshima and Nagasaki, the Marshall Islands and Three Mile Island, and Sellafield/Windscale Fire.

Solid cancers. The evidence suggests an excess risk of solid cancer incidence and solid cancer mortality among the LSS cohort and nuclear workers. However, this remains a contested finding. This review found associations in relation to Hiroshima and Nagasaki, Chernobyl, and Fukushima.

Site-specific solid cancers. Site-specific solid cancers considered to have a well-documented dose-response relationship with ionising radiation include the bladder, breast, colon, oesophagus, lung, and thyroid. There is some evidence for a dose-response relationship for bone cancer. The evidence is mixed for associations between ionising radiation and prostate, testicular, liver, and central nervous system cancers. This review found associations for Nagasaki and Hiroshima and colon, liver, lung, prostate, and kidney cancers; the Marshall Islands and Three Mile Island and oesophagus and lung cancers; and Sellafield/Windscale Fire and lung cancer.

Psychological effects. There is considerable evidence that people exposed to ionising radiation experience adverse effects on mental health, in particular PTSD, depression, anxiety, alcohol and tobacco use, and suicide. This review found associations in relation to adverse mental health and Hiroshima and Nagasaki, Chernobyl, and Fukushima.

Other non-cancer effects. The literature produced diverse findings regarding cataract; excess risk of circulatory disease; increased incidence of Parkinson's disease; some evidence that low-dose environmental exposure may be associated with higher-than-expected prevalence of antithyroid antibodies; and a possible association between chronic renal dysfunction and later cardiovascular disease mortality. This review found associations for circulatory disease and Hiroshima and Nagasaki, and Fukushima, as well as for Parkinson's disease and the Marshall Islands and Three Mile Island.

Genetic effects for exposed adults. There is mixed evidence about health effects from genetic alterations in adults exposed to ionising radiation. There is some evidence for changes in molecular markers demonstrating DNA damage, and some evidence for genomic changes in mutated genes for people who later developed MDS. This review found associations in relation to Chernobyl and Fukushima.

Genetic effects for descendants. Among 15 reviews and studies included in this review, and despite the reanalysis of data using more robust methods, none reported statistically significant findings about effects on the descendants of people exposed to ionising radiation.

INTRODUCTION

The introduction section of the report will outline the purpose for the review; key research questions that guided the review; methodology; critical appraisals for the quality assessment of reviewed literature; limitations on the body of evidence; and the report structure.

Purpose

Allen + Clarke was engaged to complete an independent systematic review of published literature to explore the physical and psychological health impacts of ionising radiation on humans and their descendants. Both veteran and civilian populations were in scope for this review.

The purpose of this piece of work was to review and summarise the most up-to-date evidence on this topic. The report is intended to be used to understand the implications of nuclear radiation exposure for New Zealand veterans and their whānau. The report will be communicated to key stakeholders and stakeholder communities, including the Minister for Veterans, Veterans' Affairs, veterans, and experts in the field.

Key research questions

The key research questions were:

1. What are the health impacts of nuclear radiation?
2. What are the health and genetic effects of nuclear radiation exposure intergenerationally on the children and descendants of those exposed?

The suggested topic areas to be reviewed included, but were not limited to:

- health impacts of nuclear testing and radiation
- genetics/epigenetics
- epidemiology
- nuclear radiation exposure
- veteran and civilian health.

Methodology

Characteristics of the review

The review adopted the following characteristics of a systematic literature review.

- Research question: began with defined research questions.
- Search method: used a search strategy or protocol with defined populations and outcomes.

- Literature search: sought all relevant literature, and utilised multiple and diverse databases.
- Inclusions and exclusions: explicit in the scope and types of documents that were included and excluded. Additionally, at least two reviewers agreed upon the framework and considered each document for inclusion or exclusion.
- Study quality: used recognised study specific guidelines (Critical Appraisal Skills Programme, CASP) to assess the quality of the literature and to conduct critical appraisal.
- Synthesis: provided a brief summary of the literature, including details regarding methodology, findings, and strength of evidence.

Search criteria

The search criteria were established in consultation with the Veterans' Health Advisory Panel. Resource parameters of time and budget were considered when developing the search criteria.

The literature search was conducted using the following search criteria:

- prioritise systematic reviews, and include select individual studies not covered by the reviews
- civilian and military populations
- physical and psychological health impacts of exposure to ionising radiation
- impacts of ionising radiation exposure intergenerationally on descendants of those exposed
- focus on ionising radiation exposure events or locations, prioritising (but not exclusive to): Hiroshima, Nagasaki, Marshall Islands, Operation Grapple, Sellafield, Three Mile Island, Chernobyl, and Fukushima
- literature published from 1990 onward
- exclude literature on non-ionising radiation and depleted uranium
- exclude literature on females and the female germline.

Databases and search terms

The following databases were searched: Scopus, PubMed, CINAHL, Embase, and PsycINFO. The search terms used were:

(military OR wartime OR atomic bomb OR atomic OR nuclear plant OR Marshall Island OR Bikini Atoll OR Operation Grapple OR Hiroshima OR Nagasaki OR Fukushima OR Chernobyl OR Sellafield OR Three Mile Island) AND (nuclear radiation OR nuclear exposure OR ionising radiation OR ionizing radiation OR alpha particle OR beta particle OR gamma particle OR radiation exposure) AND (health OR injury OR harm OR psychological OR mortality OR illness

OR disease OR cancer OR genetic OR effects OR child* OR intergeneration* OR descendant OR progeny OR hereditary) AND (veteran* OR person* OR soldier OR sailor OR airman OR people OR civilian OR survivors)

The search netted 2,317 records.

Screening and shortlisting process

Once the screening process had reduced the database from 916 to 425 records, a shortlist of 60 items was compiled, via the steps described below. The screening and shortlisting process is also illustrated below in a PRISMA diagram (Figure 1).

- A subset of the search results was established, including items from high quality journals (H Index 60+).[16] H Index categorises journals as 'good' with a score of 20 – 39; 'outstanding' with a score of 40 – 59; and 'exceptional' with a score of 60 or more. The search predominantly returned items from journals of outstanding quality (n=303).
- From the above subset, journals ranked in the Top 100 Impact Factor List for 2022 were identified, and 14 items were from these journals. These were tagged for inclusion.
- A bibliographic review was conducted on the nine systematic reviews and meta-analyses returned through the search. Items that had been returned by our search that were also covered by the systematic reviews and/or meta-analyses were removed. Systematic reviews that had been considered by subsequent systematic reviews were retained, as were two items that were particularly relevant to descendants.
- Items that specially referred to incidents of interest were identified, but there were too many (n=175) to be useful as a means of developing the shortlist. With 175 items covering at least one of the incidents of interest, it was considered reasonable to assume that the shortlist provided good coverage of the research that considers those incidents. However, it was later realised that one event, Operation Grapple, was not covered.
- An abstract review was conducted on the identified items (plus ten others initially included, but subsequently excluded). The abstract review showed 60 items to include a range of study types (systematic reviews, meta-analyses, cohort studies, and case studies); a range of study populations (atomic bomb survivors, military, nuclear workers and 'clean-up' workers, and descendants of irradiated males); material relating to health effects for descendants; material concerning psychological effects; a wide range of cancers, including solid and non-solid cancer types; genetic alteration; and non-cancer conditions/effects.

The shortlist was provided to the Veterans' Health Advisory Panel. Panellists confirmed that they were comfortable with the proposed approach, to review the shortlisted documents and then back-fill as necessary.

Through the review process, 15 of the 60 shortlisted items were found to be unsuitable. Following the review of the remaining 45 items, gaps were identified and a further 20 items

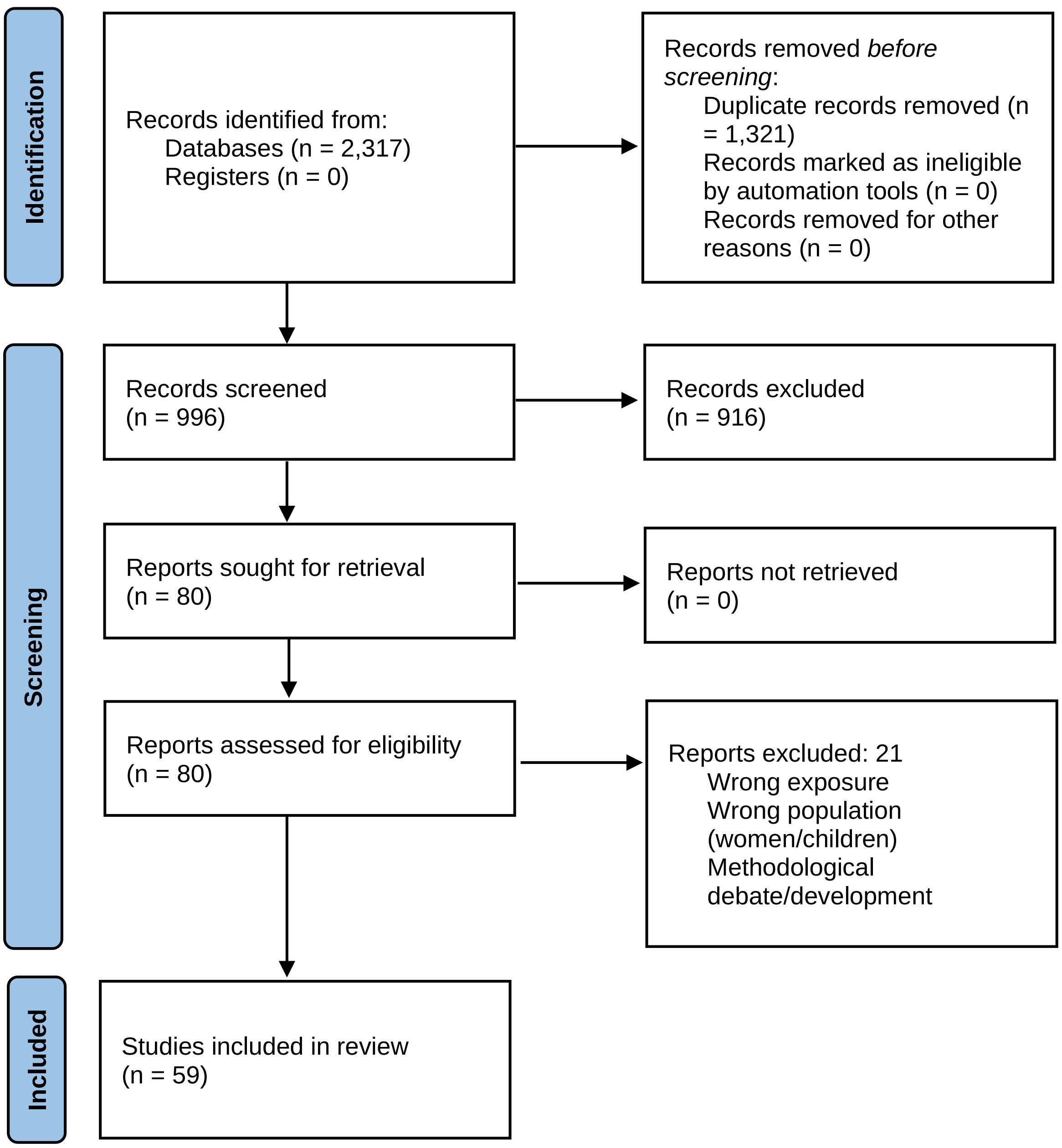
[16] https://www.cwauthors.com/article/Is-the-h-index-better-than-the-impact-factor#:~:text=The%20h%2Dindex%20value%20is,journal's%20h%2Dindex%20is%2020.

were identified amongst the 303 items identified as H Index 60+. Following a further abstract review, five were retained for inclusion in this review.

Reasons for excluding items include a focus on exposure during childhood, reviews that cover material that has been covered in more recent reviews, methodological development papers, duplicate studies, opinion pieces, items not about health effects, very small sample size, and/or other methodological issues.

The following flow diagram is a visual overview of the process used to select the included literature.

Figure 1: PRISMA diagram



Critical appraisals for quality assessment

Relevant items were subjected to critical appraisal. Critical appraisals are appended to this document, grouped by appraisal tool, and then by alphabetical order by lead author. The following Critical Appraisal Skills Programme (CASP) tools were used:

- CASP Checklist for Systematic Reviews[17] (Appendix A)
- CASP Checklist for Cohort Studies[18] (Appendix B)
- CASP Checklist for Case Control Studies[19] (Appendix C)
- CASP Checklist for Qualitative Research[20] (Appendix D)

The evidence is presented in the review following the above order, in accordance with the traditional hierarchy of evidence.

Limitations on the body of evidence

The body of evidence presents some limitations, which are briefly described below.

- Determining levels of ionising radiation is complex.
  - Exposure to ionising radiation can be measured as radioactivity released by a material, radiation in the air, absorbed radiation, and dose equivalent or effective dose.
  - Ionising radiation can be measured several different ways, including via meters or badges worn on the body (e.g., dosemeters or film badges), urine samples, and biological risk calculations.
  - Different types of radiation dose are reported using several different units. Units include the International System of Units such as Gray (Gy) and Milligray (mGy), and Sievert (Sv) and Millisievert (mSv), as well as the American units Rad and Roentgen Equivalent Man (rem and millirem). Additionally, radiation dose can be expressed as a rate, for instance Milligray per hour (mGy/h).
  - Radiation effective dose can vary by organ, as organs can have different levels of sensitivity to radiation.
  - Low, moderate, and high radiation dose exposure can have different health impacts.
  - Similarly, acute and chronic radiation exposure can have different health effects. It is noted that New Zealand Defence Force populations have been exposed to both.[21]
- Age at exposure and latency period (time since exposure) play a part in disease incidence for some conditions.

---

[17] See https://casp-uk.net/images/checklist/documents/CASP-Systematic-Review-Checklist/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf
[18] See https://casp-uk.net/images/checklist/documents/CASP-Cohort-Study-Checklist/CASP-Cohort-Study-Checklist-2018_fillable_form.pdf
[19] See https://casp-uk.net/images/checklist/documents/CASP-Case-Control-Study-Checklist/CASP-Case-Control-Study-Checklist-2018-fillable-form.pdf
[20] See https://casp-uk.net/images/checklist/documents/CASP-Qualitative-Studies-Checklist/CASP-Qualitative-Checklist-2018_fillable_form.pdf
[21] https://www.veteransaffairs.mil.nz/about-veterans-affairs/our-documents-and-publications/research/research-about-new-zealands-nuclear-veterans/

- Research about women and children exposed to ionising radiation is excluded from this literature review, as females were not deployed by the New Zealand Defence Force for the events of interest. However, all the key longitudinal cohort studies referred to in this review include females, for instance the Japanese LSS cohort is 58 percent female.
- The literature reviewed has more mortality studies than morbidity studies.
- Much of the research on ionising radiation is authored in Japan and utilises Japanese samples. It is possible that translations may result in lost or inaccurate information.
- The level of detail provided in review articles varies considerably.
- The level of information in the academic literature relating to New Zealand Defence Force personnel was limited. However, we note the following grey literature and opinion piece for Operation Grapple and the Pilaster (Mururoa) Deployment.

Operation Grapple

The health consequences of nuclear weapons testing in Kiribati, referred to as 'Operation Grapple', are overlooked in the published literature returned through the literature search, despite the term 'Operation Grapple' being specifically included. However, between 2005 and 2007 Massey University conducted three studies about New Zealand Operation Grapple veterans and ionising radiation.[22] The Sister Chromatic Exchange Study was conducted to investigate evidence of genetic damage in veterans. The Psychological Impact Study was conducted to develop a psychological profile of veterans and to investigate chronic stress and quality of life. The Cytogenetic Analysis Study was conducted to investigate genetic damage in veterans. However, in 2013 a panel of six experts reviewed the three studies and reported that "the poor choice of exposed and control subjects means that it is difficult to understand the reported differences between the groups and therefore to draw conclusions on which decisions can be made".[23] These reports were not found in our literature search because they were not published in academic literature.

Further, a recent article (Alexis-Martin et al., 2021), was accessed through a specific search for information about Operation Grapple. The opinion piece was published in *Global Policy,* which is rated by the H Index as 'good', but the reviewers note that this rating is considerably lower than the 'exceptional' rating of the literature included in this review, and so caution is advised. Alexis-Martin et al. argue that the United Kingdom (UK) government has not adequately addressed the health needs of i-Kiribati and Cook Island civilians, and military personnel from the UK, New Zealand, and Fiji. They argue that the UK Government is in breach of the 2017 Treaty on the Prohibition of Nuclear Weapons. They comment that "a culture of secrecy surrounds the tests" and they dispute claims made by the UK Ministry of Defence in 2008 that "almost all the British servicemen involved in the UK nuclear tests received little or no radiation" (Alexis-Martin et al., 2021, p. 110). Meanwhile, veterans use the term "guinea pigs" to describe their treatment, with some claiming a systematic coverup. The ongoing argument about the health effects for veterans and civilians exposed to ionising

[22] https://www.veteransaffairs.mil.nz/about-veterans-affairs/our-documents-and-publications/research/research-about-new-zealands-nuclear-veterans/
[23] https://www.veteransaffairs.mil.nz/assets/Research/00e7983c57/NZ-nuclear-tests-veterans-a-summary-of-expert-reviews-of-three-studies.pdf

radiation through Operation Grapple may in part explain its absence in the published literature about health effects.

Pilaster (Mururoa) Deployment

The Pilaster Deployment to Mururoa in 1973 is similarly overlooked in the published literature. However, in 2015 the Institute of Environmental Science and Research (ESR) completed The Radiological Review: Pilaster (Mururoa) Deployment. This review was conducted to accurately detail the extent of any radiation exposure experienced by New Zealand veterans deployed to Mururoa. In 1973 the French began a nuclear weapon testing programme at Mururoa and consequently New Zealand sent two Navy ships on a protest mission to the vicinity.[24] Comprehensive radiation monitoring programmes were in place for both ships, and during their one-month deployment New Zealand personnel witnessed the first two tests.[25] The review concluded that “the crews of HMNZS OTAGO and HMNZS CANTERBURY received no more radiation exposure during their one-month deployments to Mururoa than their families did at home, and possibly less”.[26] The ESR study was not found in our literature search because it was not published in academic literature.

Report structure

The report has two main sections, the first section presents evidence by health effects, and the second section summarises the evidence from the first section and presents the evidence by ionising radiation event or location. Before these sections begin some contextual information is briefly outlined to support reading the report.

The first section is divided into five health effect subsections: non-solid cancers, solid cancers, site-specific solid cancers, non-cancer effects, and genetic effects. Each of these five subsections include one or more related cancers or health effects. In this section, evidence is presented in alignment with the traditional hierarchy of evidence: findings from systematic reviews (with or without meta-analysis), non-systematic reviews, and literature reviews are presented first, in publication date order where necessary; followed by cohort studies; cross-sectional studies; case control studies; and then qualitative studies. No randomised controlled trials were identified.

The second section is divided into six ionising radiation event or location subsections: Hiroshima and Nagasaki, Marshall Islands and Three Mile Island, Operation Grapple, Sellafield/Windscale Fire, Chernobyl, and Fukushima. This section concludes with a table that summarises the associations (no association, uncertain association, and association) between these events or locations and health effects.

Throughout the report in-text citations are used for materials that have been reviewed, and footnotes are used for materials not included in the review.

[24] https://www.veteransaffairs.mil.nz/assets/Research/3655729163/pilaster-deployment-radiological-review.pdf
[25] Ibid
[26] Ibid

Following the conclusion and references there are four appendices to the report, one for each type of critical appraisal: systematic reviews (with and without meta-analysis), cohort studies, case control studies, and qualitative studies.

CONTEXTUAL INFORMATION

This section briefly outlines some contextual information to support reading the report. Brief descriptions are provided for the following: five longitudinal studies frequently referred to in the literature reviewed; eight events or locations prioritised in this review; the International Nuclear Event Scale; four papers frequently referred to in the literature reviewed; and the baseline understanding about the relationship between ionising radiation and cancer.

Key longitudinal studies

Five longitudinal studies were frequently referred to in the literature reviewed. These are briefly described in the table below.

Table 4: A brief description of longitudinal studies frequently referred to in this review

Adult Health Study (AHS)
A sub-sample of the Japanese Life Span Study (LSS), with about 20,000 participants at inception in 1958, and comprised of four groups matched for city, age, and sex, each similar in size. In 1977 the sample increased to about 25,400 with the inclusion of a further 2,400 LSS participants and 1,000 in utero-exposed people. The sample includes 5,000 people who were not in Hiroshima or Nagasaki at the time of the bombings and had health examinations between 1958 and 1977. The objective of the AHS is to investigate the long-term health effects of atomic bomb radiation based on biennial health examinations. Key research areas include the relationship between radiation and non-cancer diseases, the mechanism for the radiation and cancer relationship, aging and psychosocial changes, changes in physiological measurements, and medical dosimetry. The AHS sample is 36 percent male and 64 percent female. https://www.rerf.or.jp/en/programs/research_activities_e/outline_e/progahs-en/ https://www.rerf.or.jp/uploads/2017/08/TR1992-01.pdf
International Nuclear Workers Study (INWORKS)
Established in 2022 and coordinated by the International Agency for Research on Cancer (IARC), this is a collaborative epidemiological study about the health effects of protracted low-dose exposure to nuclear workers. It includes 308,297 nuclear workers, for follow-up periods of 1968-2004 (France: n=59,003), 1946-2001 (UK: n=147,866), and 1944-2005 (US: n=101,428). The study aims to use pooled analysis to increase knowledge of the risks of cancer (solid and haematological) and non-cancer diseases following chronic exposure to low-dose exposure to ionising radiation. Of specific interest is quantitative estimates of risk, via examination of the relationship between mortality and disease. Mean cumulative external dose between 1945 and 2005 was 25 mSv. The INWORKS sample is 87 percent male and 13 percent female. https://www.gov.uk/government/publications/radiation-workers-and-their-health-national-study/inworks-collaborative-study-using-nrrw-data

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4703555/pdf/nihms723379.pdf

F1: Children of Atomic Bomb Survivors

This is a cohort of roughly 77,000 people born, between May 1946 and 1984 (participants are currently aged between 38 and 76 years old), to at least one parent who was a survivor of the Hiroshima or Nagasaki atomic bomb attacks. The cohort is a managed within the RERF and the monitoring methods are the same as those used for the LSS cohort. The F1 study explores whether radiation-related abnormalities translate into birth defects or health effects in the first generation (F1) of survivors' children. The F1 sample is 51 percent male and 49 percent female.

https://www.rerf.or.jp/en/programs/research_activities_e/outline_e/progf1-en/

Japanese Life Span Study (LSS)

Established in 1958 by RERF (formerly the Atomic Bomb Casualty Commission, or ABCC), the study cohort comprises survivors from the Hiroshima and Nagasaki atomic bomb attacks. The programme investigates life-long health effects of atomic bomb radiation exposure on causes of death and cancer incidence, based on epidemiological studies (cohort and case control). About 120,000 people have been followed (82,214 from Hiroshima and 38,107 from Nagasaki), including 94,000 atomic bomb survivors and 27,0000 unexposed individuals. The LSS sample is 42 percent male and 58 percent female.

https://www.rerf.or.jp/en/programs/research_activities_e/outline_e/proglss-en/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5865006/

Million Person Study (MPS)

The Million United States Radiation Workers and Veterans Study is also referred to as the Million Person Study of Low-Dose Health Effects (MPS). The study was designed to follow people who experienced low-dose radiation over time, as a counterpart to the LSS (participants whose exposure is considered acute). The MPS is made up of five categories of workers and veterans exposed to ionising radiation between 1939 and the present: nuclear power plant workers employed from 1957 to 1984 (~145,000, including workers at the Three Mile Island nuclear power plant), industrial radiographers/non-destructive testing (~126,000), nuclear weapons test participants (~115,000 atomic veterans, including those exposed through nuclear testing in the Marshall Islands), Department of Energy workers (~360,000), and medical workers (~170,000) (Boice, Cohen, Mumma, & Ellis, 2022). The nuclear power plant worker cohort consists of 130,773 males and 4,420 females (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). The MPS sample is 97 percent male and 3 percent female.

https://www.millionpersonstudy.org/

Events or locations prioritised in this review

Eight ionising radiation events or locations were prioritised in this review. These are briefly described in the table below.

Table 5: A brief description of nuclear events included as search terms

Hiroshima	**6 August 1945**
The atomic/uranium bombing of Hiroshima (Japan) by the United States Army Air Forces (USAAF) took place on 6 August 1945. This was the first incidence of an atomic weapon being utilised in war.[27] The bomb was released from the *Enola Gay*, a USAAF plane, exploding at an altitude of 1,800-2,000 feet above Hiroshima,[28] and "with the force of more than 15,000 tons of TNT".[29] Deaths resulting from the bombing were estimated at 140,000 by the end of 1945.[30] The average dose of radiation exposure experienced by Hiroshima survivors (received above background levels of radiation, 0.005 Gy) was 0.2 Gy.[31] Commonwealth service personnel (including New Zealanders) deployed to the vicinity of the Hiroshima prefecture between 1946 and 1948. The total effective dose of ionising radiation experienced by Australian service personnel deployed in Hiroshima for the entire two-year period has been estimated to be approximately 21 mSv, or approximately 100x less than the survivors of the detonation.[32]	
Nagasaki	**9 August 1945**
Three days following the bombing of Hiroshima, the atomic bombing of Nagasaki took place.[33] A plutonium bomb was used,[34] more powerful than that used to bomb Hiroshima, but causing less damage due to the terrain.[35] Estimated deaths resulting from the Nagasaki bomb were 74,000 by the end of 1945.[36] The average dose of radiation exposure experienced by Nagasaki survivors (received above background levels of radiation, 0.005 Gy) was 0.2 Gy.[37]	
US Nuclear Weapons Test Series/Marshall Islands	**1946-1958**
Over the period between 1946 and 1958, 67 nuclear tests were conducted in the Marshall Islands by the United States of America (US). The US nuclear weapons test series was made up of several operations – including but not limited to Operation Crossroads, Operations Greenhouse and Ivy, and the Castle Bravo Test. Two of these operations were conducted to assess the effect of nuclear weapons on naval warships (Operation	

[27] https://www.britannica.com/event/atomic-bombings-of-Hiroshima-and-Nagasaki
[28] https://www.iwm.org.uk/history/the-atomic-bombs-that-ended-the-second-world-war
[29] https://www.nationalww2museum.org/war/articles/atomic-bomb-hiroshima
[30] https://www.icanw.org/hiroshima_and_nagasaki_bombings
[31] https://www.rerf.or.jp/en/faq/
[32] https://clik.dva.gov.au/system/files/media/ARPANSA%20report%20Jul%2002.pdf
[33] https://www.britannica.com/event/atomic-bombings-of-Hiroshima-and-Nagasaki
[34] https://www.icanw.org/hiroshima_and_nagasaki_bombings
[35] https://www.iwm.org.uk/history/the-atomic-bombs-that-ended-the-second-world-war
[36] https://www.icanw.org/hiroshima_and_nagasaki_bombings
[37] https://www.rerf.or.jp/en/faq/

Crossroads, 1946) and to test design features (Operation Greenhouse, 1951). Operation Crossroads was halted just over one month following its launch, due to concerns about radiation. Operation Ivy, the United States' first thermonuclear test, took place in 1952, and in 1954 the Castle Bravo Test saw the largest-scale nuclear detonation conducted by the US. Though the Marshallese residents were relocated to other islands, they still experienced nuclear radiation in the form of nuclear fallout.[38] The average external radiation doses received by adult residents varied by geographic location: southern atolls .005-.012 Gy, mid-latitude atolls .022-.060 Gy, and northern atolls between hundreds to over 2 Gy.[39]

Operation Grapple 1957-1958

Operation Grapple was a nuclear testing series led by the United Kingdom in 1957-58. Air burst tests of thermonuclear weapons (H-Bomb[40]) took place off the coast of Christmas Island and Malden Island.[41] Five hundred and fifty-one Navy personnel from New Zealand (HMNZS *Rotoiti* and *Pukaki*) were deployed to collect weather data and witness the testing.[42] Personnel wore film badges to monitor individual radiation exposure, but these were not processed due to issues storing the chemical materials required for testing. Radiation exposure was monitored through film badges on British personnel, showing very low-level radiation exposure (under 50 milliroentgens). Both New Zealand ships carried radiation monitoring apparatus on board, and "available information" suggests that there was one incidence of detected radiation on HMNZS *Pukaki*.[43] Monitoring of radioactive fallout also took place at stations at Christmas and Canton Islands, Penrhyn Island, and Apia. An Atomic Weapons Research Establishment report indicated that little fallout was recorded (less than 10 percent of the natural yearly exposure due to background radiation).[44]

Sellafield/Windscale Fire 1957

In October 1957, operators at Sellafield (formerly known as Windscale) undertook a routine annealing process to regulate Wigner energy levels in graphite moderators in Pile 1 (October 7). Annealing is a heating process conducted to release energy. The routine process did not generate temperatures high enough, and operators repeated the process with the goal to reach a temperature of 250°C (October 8). However, this resulted in overheating, reaching 400°C. Fans were ineffective in cooling the pile, and fire was

[38] https://www.atomicheritage.org/location/marshall-islands#:~:text=Between%201946%20and%201958%2C%20the,spread%20throughout%20the%20Marshall%20Islands
[39] https://dceg.cancer.gov/research/how-we-study/exposure-assessment/nci-dose-estimation-predicted-cancer-risk-residents-marshall-islands
[40] https://navymuseum.co.nz/explore/by-themes/post-war-1970/operation-grapple/
[41] https://www.veteransaffairs.mil.nz/about-veterans-affairs/our-documents-and-publications/research/research-about-new-zealands-nuclear-veterans/
[42] https://navymuseum.co.nz/explore/by-themes/post-war-1970/operation-grapple/
[43] https://www.veteransaffairs.mil.nz/about-veterans-affairs/our-documents-and-publications/research/research-about-new-zealands-nuclear-veterans/
[44] https://www.veteransaffairs.mil.nz/about-veterans-affairs/our-documents-and-publications/research/research-about-new-zealands-nuclear-veterans/

discovered, which burnt for 16 hours.[45] Water flow initiated on October 11 was used to restore the reactor to a stable temperature, which it reached on October 12. The event is variously reported as level 4 (Accident with local consequence) and level 5 (Accident with wider consequences) on the International Nuclear Event Scale (INES, described below). The event resulted in the largest accidental release of radioactive material in the history of the UK's nuclear industry.[46] England, Wales and sections of Northern Europe were contaminated by the aerial dispersal.[47] When it was realised that iodine-131 had been released into the atmosphere, the consumption of milk produced within 200 square miles was prohibited for six weeks.[48][49] It should be noted that the Windscale Fire of 1957 is not the only nuclear accident to have occurred at Sellafield. Thus, some of the items included in this review include population cohorts that predate the 1957 event.

Three Mile Island 1979

In 1979, a nuclear accident occurred at Three Mile Island resulting from a cooling malfunction causing partial melting of the core in one of the reactors. The malfunction triggered an increase in the temperature of the coolant fluid, causing the reactor to automatically shut down. The pilot-operated relief valve did not close as it was meant to, leading to the draining of much of the coolant fluid, therefore leaving residual heat in the core and causing severe damage. Operators were not immediately aware of the draining of coolant fluid as instrumentation had incorrectly displayed that the valve had closed. The accident caused the release of a small amount of radioactive material. Compressors that were used to move the radioactive gas in the days following the malfunction leaked, causing release of some radioactive gas. Most of this went through filters, except the noble gases (about 370PBq). The cause of the incident was attributed to "deficient control room instrumentation and inadequate emergency response training".[50] For the 2 million people in the area surrounding the accident, average radiation dose was estimated at 1 millirem above the natural background radiation for the area per year (100-125 millirem).[51] The accident is classified at level 5 (Accident with wider consequences) on the INES.

Chernobyl 1986

The Chernobyl nuclear accident occurred in April 1986 at a nuclear power plant near the city of Pripyat, which was part of the Soviet Union at the time. The accident eventuated from the flawed design of a reactor and mistakes made by operators. The accident caused fires and a steam explosion, resulting in the immediate death of one person and a second death due to injuries. Acute Radiation Syndrome resulting from the accident killed a further 28 people in the weeks following. Six of these were firefighters who were estimated to have received a dose of up to 20 Gy. In total, approximately 14 exabecquerel of radioactivity

[45] https://www.britannica.com/event/Windscale-fire
[46] https://www.sciencedirect.com/science/article/abs/pii/S1352231007000143
[47] http://large.stanford.edu/courses/2018/ph241/min1/
[48] https://www.radioactivity.eu.com/site/pages/Windscale_Accident.htm
[49] https://www.theguardian.com/environment/2009/apr/19/sellafield-nuclear-plant-cancer-cases
[50] https://world-nuclear.org/information-library/safety-and-security/safety-of-plants/three-mile-island-accident.aspx
[51] https://www.energy.gov/ne/articles/5-facts-know-about-three-mile-island

was released at the scene. The highest dose was received by first responders and staff at the accident scene within the same day, but a large number of liquidators tasked with radioactivity clean up in the period following received large doses of radiation (at an average of 100 mSv but ranging up to 500 mSv). Dose of populations in contaminated and radiation control areas averaged 9 mSv and 31 mSv respectively.[52] The accident is classified at level 7 (Major accident) on the INES.

Fukushima **2011**

On 11 March 2011 the Great East Japan Earthquake took place at a magnitude of 9.0. The earthquake caused a severe tsunami with a death toll of around 19,500.[53] The tsunami caused damage to the backup generators at the Fukushima Daiichi plant in northern Japan, resulting in a loss of power to the cooling systems for the reactors' cores, and thereby causing a nuclear accident. A nuclear emergency was declared, and an evacuation order was placed, originally for those within 2km of the plant, but rapidly extended to 20km. Of the 19,594 people that had worked on the site following the incident,167 received a dose over 100 mSv, with six receiving a dose over 250 mSv.[54] In Fukushima city, 65km from the Fukushima Daiichi plant, dose was recorded at 0.06 mSv/day (on 4 April 2011). There was one location beyond the 20km radius that measured 0.266 mSv/day, though surrounding areas were not as high. At the end of July, the highest recorded dose in the 30km radius was 0.84 mSv/day, 24km from the plant. The accident is classified at level 7 (Major accident) on the INES.[55]

[52] https://world-nuclear.org/information-library/safety-and-security/safety-of-plants/chernobyl-accident.aspx
[53] https://world-nuclear.org/information-library/safety-and-security/safety-of-plants/fukushima-daiichi-accident.aspx
[54] https://world-nuclear.org/information-library/safety-and-security/safety-of-plants/fukushima-daiichi-accident.aspx#:~:text=Radiation%20exposure%20and%20fallout%20beyond,health%20risk%20according%20to%20authorities
[55] https://www.iaea.org/topics/response/fukushima-daiichi-nuclear-accident

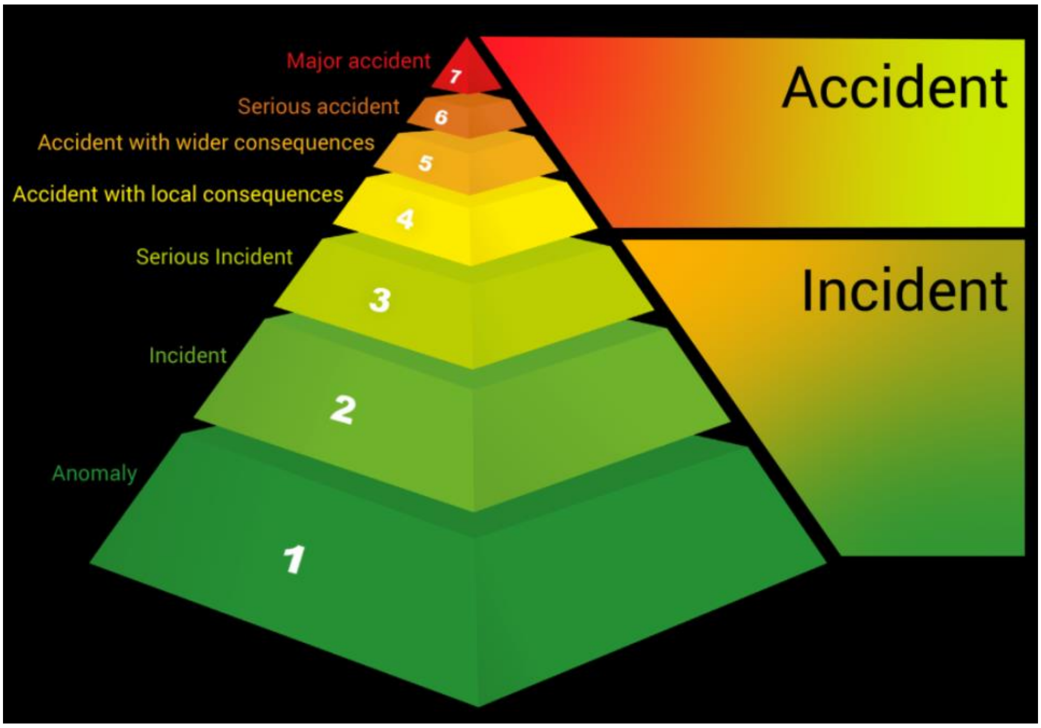
The International Nuclear Event Scale

In 1990 the International Nuclear Event Scale (INES) was developed by the International Atomic Energy Association (IAEA) and the Nuclear Energy Agency of the Organization for Economic Co-operation and Development (OECD/NEA). [56]

INES was designed to "communicate the significance of nuclear and radiological events to the public". The scale is logarithmic and has seven levels, meaning for each increase in level the severity is approximately ten times greater.

INES considers the safety significance of events in terms of their impact on (1) people and environment, (2) radiological barriers and control, and (3) defence in depth (cybersecurity).

INES is not intended for use in military applications or for applications related to medical treatments where people are intentionally exposed to radiation.



Four events considered in this research have been rated using INES as follows:

- Chernobyl, level 7
- Fukushima, level 7
- Three Mile Island, level 5
- Sellafield/Windscale Fire, levels 4 and 5

[56] https://www.iaea.org/resources/databases/international-nuclear-and-radiological-event-scale

Summaries for four key papers

Four papers were frequently referred to in the literature reviewed. These are briefly described in the boxes below.

Ruhm, Laurier, & Wakeford (2022)

Ruhm et al. (2022) synthesised and presented the epidemiological evidence of radiation-related cancer, with a focus on low-dose ionising radiation. This paper considers low-dose ionising radiation to be around 100 mGy, or a rate of <~5 mGy/h. Cohorts examined in this paper include Japanese atomic bomb survivors, nuclear workers, patients exposed for medical purposes, and populations exposed environmentally to natural background levels of radiation. Together, these cohorts consist of several million people, including many who were followed for 50 years to examine long-term impacts.

Boice, Cohen, Mumma, Golden et al. (2022)

Boice et al. (2022) conducted an extended follow-up mortality study of LANL nuclear workers. LANL workers were those who worked in a laboratory – first established during World War II – to research and design nuclear weapons. The cause of death for 15,737 workers employed between 1943 and 1980 was examined, with data from the 1940s through 2017. Two-thirds (60%) had died by 2017, a follow-up of up to 75 years. The sample was 25% female. Organ dose estimates were calculated for each worker.

Boice, Cohen, Mumma, Hagemeyer et al. (2022)

Boice et al. (2022) conducted a cohort study that used mortality data from the MPS to compute the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 nuclear power plant workers' confirmed and expected deaths. The majority (90%) of the sample experienced a cumulative dose of 10 mSv or greater (across one's career). Almost half of the sample were employed at nuclear power plants for more than 20 years. The workers were first monitored in 1957-1984 and followed through 2011. The mean duration of follow-up was 30.2 years. Causes of death evaluated were leukaemia, myelodysplastic disease, all solid cancers, oesophageal cancer, lung cancer, Parkinson's disease, and ischemic heart disease.

Ozasa, Kotaro, Shimizu, Yukiko et al. (2012)

The report by Ozasa et al. (2012) provided an overview of cancer and non-cancerous diseases amongst the 86,611 LSS cohort members for 53 years (from 1950 to 2003). The LSS cohort includes a large proportion of atomic bomb survivors who were within 2.5km of hypocentres at the time of the Hiroshima and Nagasaki bombings. The Ozasa et al. report is the 14th in a series and provides information on studies conducted in the six years since the previous report. Almost two-thirds (58%) with DS02 dose estimates had died by 2003. This report includes data from the 50,620 subjects who had died in the follow-up period. This report examines mortality from a range of causes of death, as well as dose-response relationships.

Baseline understanding about the relationship between radiation and cancer

Elaine Ron, Chief of Radiation Epidemiology at the National Cancer Institute (US) from 1997 to 2002, commented in 1998 that "radiation epidemiology is no longer needed to demonstrate that radiation causes cancer, but rather to focus on measuring the magnitude and nature of the association" (Ron, 1998, p. S30). For Ron, the fact that radiation can cause cancer was already established. From the data available to her, Ron commented it was clear "that radiation effects from the bombings persist even after 45 years of follow-up" (Ron, 1998, p. S33).

Among Japanese survivors of atomic bombings, there are well-documented dose-response relationships between radiation exposure and risks of leukaemia and solid cancers, including cancers of the bladder, breast, colon, oesophagus, lung, and thyroid (Preston et al., 2007, as cited in Li et al., 2010). This present review includes all of these cancers except for breast cancer, which is rare in men, and the risk for radiation-induced breast cancer in men is extremely small.

Having established the aforementioned introductory and contextual information the report will now present the findings about the health impacts of ionising radiation from this review.

EVIDENCE ABOUT NON-SOLID CANCERS

This section presents the evidence about non-solid cancers, specifically leukaemia, lymphoma, and multiple myeloma. Evidence is presented first by the traditional hierarchy of evidence, and second by the date of publication.

Leukaemia, lymphoma, and multiple myeloma

The literature reviewed below reports mixed findings about leukaemia, lymphoma, and multiple myeloma. Findings vary by cohort characteristics, such as age at exposure, time since exposure, and dose; and they also vary by the multiple types of disease. Overall, from this review, there appears to be more and stronger evidence of an association between exposure to ionising radiation and leukaemia, lymphoma, and multiple myeloma than for other disease conditions.

Systematic reviews, literature reviews, and other reviews (n=4)

In their synthesis of the epidemiological evidence and implications for radiological protection from low doses of ionising radiation, Ruhm et al. (2022) included three studies relating to leukaemia.

- One study focused on mortality from leukaemia and other cancers among 135,193 US nuclear power plant workers, with a follow-up period of 54 years (1957 to 2011). That study found marginal evidence for an increased risk of leukaemia except CLL amongst nuclear power plant workers who had mainly been exposed to external gamma radiation (ERR per 100 mGy: 11.5%) (Boice et al., 2021, as cited in Ruhm et al., 2022).

- A second study (Hsu et al., 2013, as cited in Ruhm et al., 2022), use LSS data to 2001, which included 312 cases of various types of leukaemia. The study found a linear dose effect in the linear-quadratic excess relative risk (ERR) model, 30 years after exposure at an attained age of 70 years, with excess risk being greatest for those exposed to radiation at a young age and within a few years of exposure. The authors noted that dose-response was stronger for acute myeloid leukaemia than for other types of leukaemia.

- The third study (Kesminiene et al., 2008, as cited in Ruhm et al., 2022) explored the risk of lympho-haematopoietic malignancies, including leukaemia (n=40), and non-Hodgkin lymphoma (NHL) (n=20), among Chernobyl liquidators (sex not specified) – most of whom received very low doses of ionising radiation as measured through red bone marrow (13 mGy). The study used two nested case control studies conducted through IARC. In their synthesis, Ruhm et al. comment that “the findings are difficult to interpret”, with an estimated ERR per Gy for leukaemia (excluding chronic lymphocytic leukaemia (CLL)) of 5.0 (95% CI: - 5.5, 67); whereas the ERR per Gy for CLL was 4.7 (95% CI: <0, 90), and for NHL, it was 28.1 (95% CI: -4.3, 284) (Kesminiene et al., 2008, as cited in Ruhm et al., 2022, p. 9).

Hauptmann et al. (2020) conducted a meta-analysis of 20 studies (also described in the section of this report about solid cancers) exploring leukaemia risk following exposure to low-dose ionising radiation (mean cumulative dose <100 mGy) in adulthood (males and females combined). The meta-analysis resulted in a summary risk estimate for adult exposure of 0.16, which the authors remarked to be double that found from the LSS (0.8 at 100 mGy) but very similar to the results of another meta-analysis of 10 studies of protracted exposure to low-dose radiation (Daniels & Schubauer-Berigan, 2011, as cited in Hauptmann et al., 2020).

A meta-analysis modelled 10 observational studies (sex not specified), adjusting for publication bias, synthesising information to calculate an aggregate estimate to the ERR from protracted exposure to low-dose ionising radiation (ERR at 100 mGy of 0.19 (95% CI: 0.07, 0.32)) (Daniels et al., 2011). Selected studies were limited to adult populations exposed through occupational and environmental settings: medical therapy patients were excluded. Daniels et al. concluded that:

> *Leukemia (excluding CLL) is significantly associated with exposure to protracted, low-level ionizing radiation … [with an] estimate of leukemia risk at 100 mGy of 0.19 (95% CI: 0.07; 0.32). … All model results were in reasonable agreement with the leukemia risk observed in atomic bomb survivors, which is regarded by most as the gold standard" (Daniels et al., 2011, p. 463).*

An IARC study published in 1994 (also described in the section of this report about solid cancers) combined incidence and mortality data from seven nuclear facilities across Canada, the UK, and the US to determine if assumptions about the calculation of protection measures were adequate (IARC Study Group on Cancer Risk among Nuclear Industry Workers, 1994). The pooled data accounted for 95,673 nuclear workers, 15,825 of whom had died within the study period, which commenced between 1944 and 1956 and concluded between 1979 and 1988. 119 deaths were from leukaemia excluding CLL, resulting in an ERR of 2.2 per Sv (90% CI: 0.1; 5.7). Calculations using the pooled data were compared with those from the data of Japanese atomic survivors, resulting in author confidence that protection measures were being adequately calculated. The authors concluded:

> *The estimates are the most precise yet to have been obtained directly from populations with protracted exposures to low levels of X and ɣ radiation. They suggest that the risk estimates obtained by extrapolation from the studies of atomic bomb survivors are unlikely to be substantially in error (IARC Study Group on Cancer Risk among Nuclear Industry Workers, 1994, p. 1041).*

Cohort studies (n=9)

Mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 workers' confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). Mean absorbed dose varied by organ but ranged between 33.2 mGy (brain) and 43.9 mGy (heart). For leukaemia (other than CLL) there were 296 deaths, resulting in a standardised mortality rate (SMR) of 1.06 (95% CI: 0.94, 1.19). This means that prolonged exposure to radiation increased the risk of leukaemia (except CLL) among nuclear power plant workers. Boice et al. noted these findings to be consistent with other studies, and that "prolonged exposure to occupational radiation was seen to increase the mortality risk of leukemia other than CLL among NPP [nuclear power plant] workers" (Boice, Cohen, Mumma, Hagemeyer, et al., 2022, p. 668). They further noted that there appeared to be different risks through acute exposure compared to chronic exposure: "the acute exposure of atomic bomb survivors may carry a somewhat higher risk of radiation-induced leukemia than the study of NPP workers who received prolonged exposures over many years" (Boice, Cohen, Mumma, Hagemeyer, et al., 2022, p. 669). Boice et al. found neither myelodysplastic syndromes (MDS) nor MDS in combination with acute myeloid leukaemia (AML) to be correlated with radiation dose, which they noted to be like other studies but in contrast to findings from studies of the LSS. Nor did they find any correlation to CLL, which was consistent with other studies and contrary to findings from the LSS.

Boice et al. (Boice, Cohen, Mumma, Golden, et al., 2022) conducted an extended follow-up mortality study on workers at the Los Alamos National Laboratory, New Mexico, United States (LANL). The cause of death for 15,737 workers was examined, with data from the 1940s to 2017. They found "no evidence for a radiation-related excess of NHL among the LANL employees" (Boice, Cohen, Mumma, Golden, et al., 2022, p. 739). With 130 deaths through leukaemia (excluding CLL), risk was not significantly elevated, at ERR per 100 mGy of -0.43 (95% CI: -1.11, 0.24).

A secondary analysis of a cohort from the LSS (n=533) was conducted, aligning leukaemia diagnoses made between 1950 and 1994 with the current World Health Organization (WHO) classification of tumour subtypes (Fujihara et al., 2022). The study brought historical cases into the present histological subtypes, strengthening the evidence base about the relationship between exposure to ionising radiation and haematological malignancies. Fujihara et al. found "a significant dose response for males with an ERR/Gy of 0.95 (95% CI: 0.25, 1.93)" (Fujihara et al., 2022, p. 223). However, they did not find statistically significant evidence of radiation effects for either mature B-cell neoplasms or mature T-/NK-cell neoplasms.

A study screening for M-Proteinemia and monoclonal gammopathy of undetermined significance (MGUS) (Fujimura et al., 2021) found no statistically significant association between radiation exposure category and M-Proteinemia prevalence or MGUS incidence. They did find a significantly higher risk of M-proteinemia at 70 years and MGUS for males and people less than 20 years old at the time of exposure. Fujimura et al. concluded that exposure to environmental factors at a young age may be important to developing MGUS in later life.

Hayashi et al. (2021) found that it was possible to detect raised levels of reactive oxygen species in blood cells in those exposed to a high-dose radiation 60 years prior (atomic bomb survivors). They found that those exposed to high-dose radiation may have decreased immune function, increased inflammatory states, and increased reactive oxygen species in their blood cells, although the link to disease conditions was not established.

Taguchi et al. (2020) conducted genome analysis on survivors of the nuclear bomb dropped at Nagasaki to identify MDS. They conducted this analysis on 35 people diagnosed with MDS and divided the sample into groups based on exposure. Those who were within 2.7km of the detonation site were the exposure group (proximal) and those further away were considered the controls among this sample (distal). The main finding of this study is that MDS survivors exposed to atomic bomb radiation have genetic alterations (11q deletions and aberrations) but further research was needed to understand the role these genetic alterations play in developing MDS after radiation exposure (Taguchi et al., 2020, p. 361).

A study by the UK National Registry for Radiation Workers (Gillies et al., 2019, as cited in Boice, Cohen, Mumma, Hagemeyer, et al., 2022) including 174,541 occupationally exposed workers (mean dose 25.5 mSv), found a significant risk of leukaemia other than CLL, with an ERR per Sv of 1.38 (90% CI: 0.08, 3.24). Boice et al. noted that more than half of the workers with high cumulative doses (>100 mSv) worked at Sellafield.

The data of radiation-monitored workers from France (n=59,003), the UK (n=147,866) and the US (n=101,428) were pooled, creating INWORKS (Leuraud et al., 2015). The data collectively accounted for 8.22 million person-years of follow-up, with a mean follow-up of 27 years. Of the 531 deaths recorded as caused by leukaemia excluding CLL, 53 percent of these deaths were workers exposed to less than 5 mGy. “The estimated ERR of mortality caused by leukemia excluding CLL was 2.96 per Gy (90% CI 1.17-5.21)” (Leuraud et al., 2015, p. e279). The study found positive associations for chronic myeloid leukaemia (ERR/Gy 10.45, 90% CI: 4.48, 19.65), acute myeloid leukaemia (ERR/Gy 1.29, 90% CI: -0.82, 4.28) and acute lymphoblastic leukaemia (ERR/Gy 5.80, 90% CI: not estimable, 31.57). Less-precise associations were also found for Hodgkin’s lymphoma, NHL, and multiple myeloma. The authors noted their findings to be similar in size and precision to those from LSS studies. They concluded that their study “provides strong evidence of an association between protracted low-dose radiation exposure and leukemia mortality” (Leuraud et al., 2015, p. e280).

A study of MDS risk 40 to 60 years after high-dose radiation exposure (Iwanaga et al., 2011) found a significant linear relationship between radiation dose and MDS risk among atomic bomb survivors. MDS rates were higher for men than for women and increased with age at exposure to radiation. The bone marrow weighted dose for approximately 60 percent of the cohort was less than 0.005 Gy. MDS rates also increased with increased estimated dose (ERR/Gy 4.3 (95% CI: 1.6, 9.5)) and proximity (ERR decay per km 1.2 (95% CI: 0.4, 3.0)) to the hypocentre. The retrospective study identified patients presenting with MDS at five hospitals in the Nagasaki region between 1982-2004 and created control and radiation exposure groups by linking the data with the Atomic Bomb Disease Institute (ADBI) Data Centre and the LSS. The authors concluded that long term follow-up should be conducted for people who have been exposed to high-dose radiation “to detect MDS as early as possible and reduce the risk of leukemic transformation” (Iwanaga et al., 2011, p. 434).

EVIDENCE ABOUT SOLID CANCERS

This section presents the evidence about solid cancers all together, whilst the next section presents the evidence about solid cancers by site. Evidence is presented first by the traditional hierarchy of evidence, and second by the date of publication.

> There is a body of evidence suggesting an excess risk of solid cancer and solid cancer mortality among the LSS cohort and nuclear workers. However, this remains a contested finding.

Boice et al. (2022) noted that the practice of estimating radiation associations for all solid cancers together is frequently done for statistical precision and is valuable, but lacks biological plausibility due to heterogeneity in cancer types (National Council on Radiation Protection and Measurements, 2012, as cited in Boice, Cohen, Mumma, Hagemeyer, et al., 2022).

Systematic reviews, literature reviews and other reviews (n=3)

The synthesis conducted by Ruhm et al. (2022) described an analysis of 29 epidemiological studies that used the linear non-threshold model, which aims to determine radiation dose-response to estimate stochastic health effects, conducted by the US National Council on Radiation Protection. The analysis rated the quality of those 29 studies, which Ruhm et al. report as follows:

> *In general, study-size constraints, dose uncertainties and epidemiological weaknesses of low dose studies limit the statistical power and precision of risk estimates, especially for data below 100 mGy. Nevertheless, the report demonstrates that the majority of evaluated low dose studies show strong, moderate, or weak-to-moderate consistency with the LNT model, for total solid cancer and for leukemia. Only five studies showed no support to the LNT model, while four studies were considered inconclusive (National Council on Radiation Protection and Measurements, 2018; Shore et al., 2018, as cited in Ruhm et al., 2022).*

The synthesis of Ruhm et al. (2022) included:

- an analysis from INWORKS with 308,297 nuclear workers (87 percent male). The INWORKS analysis showed that of the 66,632 known deaths which occurred before the end of follow-up, 17,957 were due to solid cancers (Richardson et al., 2015, as cited in Ruhm et al., 2022). Using a linear dose-response model, they found an ERR per Gy of 0.48 (95% CI: 0.15, 0.85), which is statistically significant. Leuraud et al. state that their study "provides a direct estimate of the association between protracted low dose exposure to ionizing radiation and solid cancer mortality" (Leuraud et al., 2021, as cited in Ruhm et al., 2022, p. 6).

- a study of data from the UK national registry for radiation workers, focusing on data from 1955 to 2011 (n=167,003), which explored cancer mortality, considering exposure incidence and dose. The study, by Haylock et al., found a "radiation-related solid cancer mortality ERR/Sv of 0.24 (95% CI: -0.03, 0.53)Sv^{-1}" (Haylock et al., 2018, as cited in Ruhm et al., 2022, p. 11). Haylock et al. noted the consistency of their findings with those from LSS studies, concluding that their study "provides direct evidence of cancer risk from low dose and dose rate occupational external radiation exposures, … [and that] overall rates are consistent with the risk estimates from the LSS" (Haylock et al., 2018, as cited in Ruhm et al., 2022, p. 11). This means that the study by Haylock et al. suggests that UK radiation workers are more likely than their unexposed peers to die due to some form of solid cancer.

- a follow-up study of Chernobyl clean-up workers (n=69,440), covering the years 1992 to 2017, found 6,981 cases of solid cancers, with 4,272 deaths from solid cancers. "The ERR/Gy estimates for the entire 1992-2017 period were significantly raised at 0.48 (approximate 95% CI: 0.1, 0.8) for solid cancer incidence and at 0.67 (approximate 95% CI: 0.2, 1.2) for solid cancer mortality" (Ivanov et al., 2020; and Cologne et al., 2018) as cited in Ruhm et al., 2022, p. 11).

Hauptmann et al. (2020) conducted a systematic review of 26 studies all published after the US National Research Council 2006 review *Biological Effects of Ionizing Radiation.* Hauptmann et al. assessed the magnitude of the risk of excess cancer (solid cancers and leukaemia) from ionising radiation, exploring the results to determine if bias may explain the excess risk. They concluded from their study that:

> *There is now a large body of epidemiological data that supports excess cancer risks for low-dose ionizing radiation, and the magnitude of the excess relative cancer risk from these low dose studies is statistically compatible with the atomic bomb survivors (Hauptmann et al., 2020, p. 199).*

The meta-analysis by Hauptmann et al. resulted in a summary risk estimate at 100 mGy of 0.029 (95% CI: 0.011, 0.047) for solid cancers, for adulthood exposure. The authors remarked that this was "very similar to the recent estimate from the Life Span Study [LSS] for males of 0.027 at 100 mGy" (Hauptmann et al., 2020, p. 194). This result suggests excess solid cancer risk for adults exposed to ionising radiation.

An IARC study published in 1994 (also described in the section of this report about leukaemia), combined incidence and mortality data from seven nuclear facilities across Canada, the UK and the US to determine if assumptions about the calculation of protection measures were adequate (IARC Study Group on Cancer Risk among Nuclear Industry Workers, 1994). The pooled data accounted for 95,673 nuclear workers, 15,825 of whom had died within the study period which commenced between 1944 and 1956, and concluded between 1979 and 1988. Roughly 25 percent of deaths were attributed to cancers excluding CLL (n=3,830) resulting in an ERR of -0.07 per Sv (90% CI: -0.4; 0.3). This result suggests excess risk for death from all cancers excluding CLL for nuclear industry workers. Calculations using the pooled data were compared with those from the data of Japanese atomic survivors, resulting in author confidence that protection measures were being adequately calculated. The authors concluded:

> *The estimates are the most precise yet to have been obtained directly from populations with protracted exposures to low levels of X and y radiation. They suggest that the risk estimates obtained by extrapolation from the studies of atomic bomb survivors are unlikely to be substantially in error (IARC Study Group on Cancer Risk among Nuclear Industry Workers, 1994, p. 1041).*

In a Review Series commissioned by The Lancet, *From Hiroshima and Nagasaki to Fukushima 1,* the authors noted that "survivors have a dose-response relation that is linear for solid cancer, but that is still unclear at low doses" (Kamiya et al., 2015, p. 469).

Cohort studies (n=3)

Mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 workers' confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). The authors reported a solid cancer ERR per 100 mGy of 0.01 (95% CI: -0.05, -0.05) and noted that their estimate was consistent with the LSS estimate for 100 mGy of 0.042 (95% CI: 0.032, 0.053) (Ozasa et al., 2012, as cited in Boice, Cohen, Mumma, Hagemeyer, et al., 2022). However, for all solid cancers, they found "little evidence of a dose-response relationship" (Boice, Cohen, Mumma, Hagemeyer, et al., 2022, p. 671). The authors concluded that they found "little evidence for a radiation association for all solid cancers" (Boice, Cohen, Mumma, Hagemeyer, et al., 2022, p. 657).

Otani et al. (2022) investigated the association between residual radiation exposure and mortality linked to solid cancers among a sample of individuals living in Hiroshima who were registered as nuclear bomb survivors (n=45,809). The study found that: "middle-aged people who entered the city on the day of the bombing were exposed to higher levels of residual radiation than other age groups, and their ERR of solid cancer mortality was significantly higher than that of the control group" (Otani et al., 2022, p. 51).

A report by Ozasa et al. (2012) provided an overview of cancer and non-cancerous diseases amongst the LSS cohort for 53 years (from 1950 to 2003). The report is the 14th in a series and provides information on studies conducted in the six years since the previous report. The authors stated "the most important finding regarding the late effects of A-bomb radiation exposure on mortality is an increased risk of cancer mortality throughout life" (Preston et al., 2003, as cited in Ozasa et al., 2012, p. 229). They noted, however, that being exposed in childhood increased the relative risks for many cancers. For solid cancers, although relative risk declined as people got older, the excess absolute rates continued to increase with a dose-response relationship and an ERR per Gy of 0.42 (95% CI: 0.32, 0.53) at age 70 after exposure at age 30.

EVIDENCE ABOUT SITE-SPECIFIC SOLID CANCERS

The previous section presented the evidence about solid cancers all together. This section presents the evidence about solid cancers by site, specifically bone; central nervous system; colorectal; oesophageal; liver, biliary tract, and pancreatic; lung; prostate; testicular; thyroid; and urinary tract. Evidence is presented first by the traditional hierarchy of evidence, and second by the date of publication.

Site-specific solid cancers considered to have a well-documented dose-response relationship with radiation exposure include the bladder, breast, colon, oesophagus, lung, and thyroid (Preston et al., 2007, as cited in Li et al., 2010). In this review, this list is supplemented by bone cancer, for which there is some evidence suggesting a dose-response relationship. There were mixed results for prostate cancer and testicular cancer; and a sizeable portion of post-mortem liver cancer diagnoses are shown to be possibly erroneous. On the other hand, some of the literature has found uncertainty about dose-response, such as cancers of the central nervous system.

Bone cancer

Cohort studies (n=1)

Boice et al. (2022) conducted an extended follow-up mortality study on workers at the LANL. Cause of death for 15,737 workers were examined, with data from 70 years (from the 1940s to 2017). Twelve workers from the LANL had died from bone cancer, and there was “a small but statistically significant increase in bone cancers among the workers monitored for plutonium” (Boice, Cohen, Mumma, Golden, et al., 2022, p. 738). The authors reported an SMR of 2.44 (95% CI: 0.98, 5.03) and that plutonium dose was related to an increase of bone cancer.

Central nervous system cancers

Systematic reviews, literature reviews, and other reviews (n=1)

A synthesis (Ruhm et al., 2022) reported that a study of the 2017 LSS data with a follow-up period of 50 years identified 287 tumours of the central nervous system. The study subsequently reported a linear dose-response model with an ERR per Gy of 1.40 (95% CI: 0.61, 2.57). Although they found a statistically significant dose-response for some tumour types (glioma and meningioma), they concluded by emphasising that there was substantial uncertainty in dose-response (Brenner et al., 2020, as cited in Ruhm et al., 2022).

Colorectal cancer

Systematic reviews, literature reviews, and other reviews (n=2)

A synthesis (Ruhm et al., 2022) reported that a study of the 2017 LSS data, which included 2,960 colorectal cancer cases (includes 1,046 rectal cancers), found a significant dose-response for colon cancers, but not for rectal cancer (Sugiyama et al., 2020, as cited in Ruhm et al., 2022). Specifically, the authors found elevated risk at 0.2-0.5 Gy and higher dose.

An invited supplementary article, (Ron, 1998), noted that amongst atomic bomb survivors “for colon cancer incidence, males have almost double the dose specific ERR of females, and there is little evidence that the ERR depends on age at exposure” (Pierce et al., 1996, and Preston et al., 1994, as cited in Ron, 1998, p. S33).

Cohort studies (n=2)

A study by Bockwoldt et al. (2021) investigated the relationship between exposure and survival after cancer diagnosis. Data was collected from 7,728 patients who had been exposed to ionising radiation (LSS cohort) prior to their diagnosis with invasive stomach, colon, or rectal cancers. Most of the patients were under the age of 40 years at the time of exposure; they were mostly exposed to 0.005-0.49 Gy; few were diagnosed before the age 60 years, and most were diagnosed between 70 and 79 years. Bockwoldt et al. observed that “radiation dose was not significantly associated with disease-specific survival, regardless of cancer site” (Bockwoldt et al., 2021, p. 416). However, when the data were examined for all sites, stratified by stage at diagnosis (which was not always possible, due to missing data), they found higher levels of exposure (≥1 Gy) to be “suggestively associated with poorer survival … however this association was significant for rectal cancer only” (2021, p. 416).

A study by Semmens et al. (2013) explored the relationship between colon cancer, body mass, and other anthropomorphic factors in atomic bomb survivors (n=56,064). Most of the sample were exposed as adults. The authors found a linear dose-response for radiation and colon cancer and reported an ERR per Gy of 0.53 (95% CI: 0.25, 0.86). Additionally, Semmens et al. (2013) found that, although both radiation exposure and being overweight (Body Mass Index of ≥ 25) are risk factors for colon cancer, there was no association: instead, these factors act independently.

Liver, biliary tract, and pancreatic cancers

Systematic reviews, literature reviews, and other reviews (n=2)

A study of the 2017 LSS data included 2,016 liver cancers, 694 biliary tract cancers, and 723 pancreas cancers. The study found that risk increased with dose, especially for women, for pancreatic cancer; a significantly elevated ERR per Gy for liver cancer, with no evidence for curvature in the dose-response; and that radiation dose was not associated with biliary tract cancer (Sadakane et al., 2019, as cited in Ruhm et al., 2022).

A report by Ozasa et al. (2012) provided an overview of cancer and non-cancerous diseases amongst the LSS cohort for 53 years (from 1950 to 2003). The authors reported that the risk of liver cancer mortality was statistically significantly increased for both males and female atomic bomb survivors. The sex-averaged ERR per Gy was 0.38 (95% CI: 0.11, 0.62) for liver cancer.

Cohort studies (n=2)

Boice et al. (2022) conducted an extended follow-up mortality study on workers at the LANL. Cause of death for 15,737 workers were examined, with data from the 1940s to 2017. They found “no evidence for an increased risk of liver cancer related to external or internal plutonium doses” (Boice, Cohen, Mumma, Golden, et al., 2022, p. 737). The ERR at 100 weighted-mGy was -0.01 (95% CI: -0.14, 0.12, n=110). Boice et al. noted that this finding contrasted with those from the LSS, amongst whom liver cancer has been found to be significantly increased.

French et al. (2020) asserted that there are difficulties in diagnosing primary liver cancer at death, because cancer metastases to the liver from nearby organs. Their research sought to estimate the extent to which liver cancer may be misdiagnosed as the primary cancer and inaccurately attributed as cause of death. French et al. used data simulations “to quantify the potential impact of death-certificate inaccuracies on radiation risk estimates” for primary liver cancer (2020, p. 1295). Of 1,885 cases of primary liver cancer in the LSS, 383 were diagnosed only on the basis of death certificate. Through their data simulation, they estimated that between 256 and 279 of the 383 ‘death certificate’ diagnoses were correct, suggesting that between 104 and 127 death certificate diagnoses were false positives. Their data suggested, but this was not overt, that an ERR for liver cancer based solely on Japanese LSS data may be exaggerated.

Lung cancer

Systematic reviews, literature reviews, and other reviews (n=2)

Amongst the atomic bomb survivors’ cohort in the LSS, an intriguing finding emerged. Amongst 2,446 lung cancer cases investigated between 1959 and 2009, there was a complex dose-response relationship observed for people with a history of smoking: the ERR per Gy for low to moderate smokers was significantly higher than for heavy smokers (Cahoon et al., 2017, as cited in Ruhm et al., 2022, p. 4). This result indicates that there is a significantly higher elevated risk of lung cancer for low-moderate smokers compared to heavy smokers. Ruhm et al. commented that the findings required further investigation.

A study of 45,817 nuclear workers from Mayak and Sellafield found “ERR/Gy estimates for external exposure for the two combined workforces ranged from 0.30 (95% CI: 0.10, 0.56) for lung cancer incidence (893 cases) to 0.39 (95% CI: 0.20, 0.60) for lung cancer mortality (1,195 deaths) … the ERR was found to be significantly raised at doses of 300-400 mGy” (Gillies et al., 2017, as cited in Ruhm et al., 2022, p. 6). The authors also found evidence for a linear dose-response. This result indicates that at doses of 300-400 mGy there was an elevated risk of lung cancer incidence and mortality for nuclear workers.

Cohort studies (n=2)

Mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 workers’ confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). Boice et al. found lung cancer to be significantly elevated among their sample compared to the general population, with an SMR of 1.10 (95%

CI: 1.07, 1.14). They hypothesised that this may be due to cigarette smoking and/or occupational exposure to asbestos. Nevertheless, there was "little evidence for a radiation dose response for lung cancer" among their sample (Boice, Cohen, Mumma, Hagemeyer, et al., 2022, p. 670).

Boice et al. (2022) conducted an extended follow-up mortality study on workers at the LANL. Cause of death for 15,737 workers were examined, with data from the 1940s to 2017. "There were 836 deaths due to lung cancer, and no evidence for increasing risk with radiation dose, regardless of applying radiation weighting factors for plutonium of 1, 10 or 20" (Boice, Cohen, Mumma, Golden, et al., 2022, p. 736). This result reveals a lack of evidence for radiation increasing lung cancer risk among nuclear workers.

Oesophageal cancer

Systematic reviews, literature reviews, and other reviews (n=1)

A report by Ozasa et al. (2012) provided an overview of cancer and non-cancerous diseases amongst the LSS cohort for 53 years (from 1950 to 2003). The authors reported that the risk of cancer mortality increased for the oesophagus, however the result reached statistical significance for females only. For males, the ERR per Gy was 0.39 (95% CI: -0.006, 0.97), and for females was 1.1 (95% CI: 0.04, 3.0).

Cohort studies (n=2)

A study of mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to low-dose radiation amongst 29,076 workers' confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). The mean cumulative dose to the oesophagus was 41.6 mGy (with a maximum of 1.05 Gy). Boice et al. found cancer of the oesophagus to be elevated when compared to the general population, but this was not statistically significant, with an SMR of 1.07 (95% CI: 0.96, 1.19). As well as a dose-response ERR for oesophageal cancer at 100 mGy of 0.11 (95% CI: -0.05, 0.28). The authors concluded that "cancer of the esophagus was elevated and there was suggestion of a dose-response" (Boice, Cohen, Mumma, Hagemeyer, et al., 2022, p. 672).

Boice et al. (Boice, Cohen, Mumma, Golden, et al., 2022) conducted an extended follow-up mortality study on nuclear workers first employed at the LANL between 1943 and 1980. After examining the cause of death for 15,737 workers they reported that "a significant association was seen between estimated dose to the esophagus and radiation among LANL workers. The mean dose to esophagus was 12.8 mGy and the maximum was 858 mGy" (Boice, Cohen, Mumma, Golden, et al., 2022, p. 739). The ERR per 100 mGy was 0.29 (95% CI: 0.02, 0.55). This result suggests elevated risk of death from oesophageal cancer for nuclear workers exposed to radiation compared to unexposed counterparts.

Prostate cancer

Systematic reviews, literature reviews, and other reviews (n=1)

A synthesis (Ruhm et al., 2022) has reported that a 2017 study of the LSS data included 851 prostate cancer cases from amongst 41,455 male survivors. The study reported a statistically significant ERR per Gy of 0.57 (95% CI: 0.21, 1.00) (Mabuchi et al., 2021, as cited in Ruhm et al., 2022). Additionally, the authors found a significant linear dose-response: “the observed dose response strengthens the evidence of a radiation effect on the risk of prostate cancer incidence in atomic bomb survivors” (Mabuchi et al., 2021, as cited in Ruhm et al., 2022, p. 5).

Cohort studies (n=1)

Mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 nuclear workers’ confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). Boice et al. found no elevation in prostate cancer among their sample, the SMR based on 527 deaths was 0.99 (95% CI: 0.91, 1.08).

Testicular cancer

Systematic reviews, literature reviews, and other reviews (n=1)

Yousif et al. (2010) concluded that “an association between ionizing radiation exposure and development of testicular cancer could not be convincingly demonstrated” (2010, p. 400). The evidence they reviewed is briefly summarised below.

A literature review of 31 studies (including a study of New Zealanders exposed through British nuclear testing in the Pacific) was conducted about ionising radiation effects on testicular cancer (Yousif et al., 2010). Yousif et al. noted that two good quality cohort studies of radiation workers “did not show an increase in either incidence or mortality rates of testis cancer” (Ritz, 1999, McGeoghegan & Binks, 2000, as cited in Yousif et al., 2010, p. 394). Further, three high quality studies showed “no increase in the standard registration rate (used to compare cancer morbidity – registration rates – in different populations in a specific time period) SRR (0.73 and 0.92) for testicular cancer in radiation workers … or after plutonium exposure” (Douglas, Omar & Smith, 1994, Geoghegan & Binks, 2000, and Omar, Barber & Smith, 1999, as cited in Yousif et al., 2010, p. 394).

- Among workers in nuclear power plants, a study, deemed by Yousif et al. to be of low quality, showed an increase in testicular cancer. However, Yousif et al. noted that workers were exposed to other hazards in addition to radiation (Whorton et al., 2004, as cited in Yousif et al., 2010). In contrast, four studies rated as high quality and one rated as moderate quality all showed there to be no significant increase in testis cancer risk after exposure to ionising radiation (Boice at al., 2006, Cardis et al., 2007, Loomis & Woolf, 1996, Atkinson et al., 2004, McGeoghegan & Binks, 2000, and Frome et al., 1997, as cited in Yousif et al., 2010).
- Regarding mortality, Yousif et al. reported that a cohort study had found an elevated SMR, but only four cases were included in that study (Douglas, Omar and Smith, 1999, as cited in Yousif et al., 2010). Among radiation workers at the LANL, a 30-year follow-up study did not show any increase in SMR (Wiggs et al., 1994, as cited in Yousif et al., 2010).
- Among military personnel, no increase in testicular cancer incidence or mortality was observed in a study of exposed Royal New Zealand Navy personnel (Pearce et al., 1990, as cited in Yousif et al., 2010). Contrastingly, a cohort study of their British counterparts,

rated as high quality, observed a non-significant increased relative risk (RR) for testicular cancer (RR 1.23; 90% CI: 0.27, 5.91) (Darby et al., 1993, as cited in Yousif et al., 2010).

- Among flight personnel, Yousif et al. reported that "good quality studies showed a non-significant increase in incidence as well as mortality from testicular cancer associated with cosmic radiation" (Yousif et al., 2010, p. 398).
- Among health practitioners exposed through their practice, variable results had been found in studies of testicular cancer incidence and mortality. A good quality study from the US showed no increased mortality, but a low quality Canadian study found a non-significantly increased SMR (Mohan et al., 2003, and Zielinksi et al., 2005, as cited in Yousif et al., 2010).
- Studies of testicular cancer incidence and mortality associated with exposure to ionising radiation through electromagnetic fields have suggested a possible association. However, Yousif et al. concluded that the high quality studies in this group had shown no such association in relation to either incidence or mortality (Yousif et al., 2010, p. 400).

Thyroid cancers

Systematic reviews, literature reviews, and other reviews (n=2)

A meta-analysis described how Lithuanian workers who contributed to the Chernobyl clean up (n=6,707) were followed up from their return from Chernobyl through to 2012. The study observed a statistically significant standardised incidence ratio of 3.13 (95% CI: 1.3, 7.52) among workers who were aged less than 30 years at the time of exposure to doses greater than 100 mSv (Smailyte et al., 2021, as cited in Ruhm et al., 2022). This means that clean-up workers aged less than 30 years were at higher risk of thyroid cancers compared to their unexposed peers and older clean-up workers.

A literature review by Ron (2007) covered studies of people living in Belarus, Russia, and Ukraine who were exposed to environmental ionising radiation from the Chernobyl accident found that the data on adult exposure was limited and inconsistent. The author noted that in most of the studies thyroid cancer risk appeared to decrease with increasing age at exposure, and there were no significant differences in the radiation-related relative risk between men and women, but that more women developed thyroid cancers. The evidence was inconsistent on the impact of iodine deficiency, with some studies reporting it enhancing risk of thyroid cancers, and others finding no effect.

Cohort studies (n=1)

Li et al. (2010) used the LSS data to explore the relationship between first and second primary cancers. Of the 77,752 atomic bomb survivors, 14,048 were diagnosed with a primary cancer of whom 1,088 were diagnosed with a second primary cancer. Li et al. found radiation to be related to both first and second primary thyroid cancer, and that survivors of thyroid cancer as a first primary cancer were at a strong risk of developing a second primary cancer.

Case control studies (n=1)

The risk of thyroid cancer amongst Chernobyl liquidators, most of whom received very low doses of radiation, was explored in two nested case control studies conducted through IARC.

107 cases were studied with a median total (external and internal) thyroid dose of 69 mGy. A statistically significant dose-response relationship was found when dose was 300 mGy or more, with an estimated ERR per Gy of 3.8 (95% CI: 1.0, 10.9) (Kesminiene et al., 2012, as cited in Ruhm et al., 2022). Ruhm et al. commented that this finding is “puzzling given that little evidence for an excess risk of thyroid cancer after exposure to radiation during adulthood exists in the literature” (2022, p. 9).

Urinary tract cancers

Cohort studies (n=4)

Drawing on the data from the LSS gathered across a 52 year period (between 1958 and 2009), Grant et al. (2021) examined urinary tract cancer (UTC) and kidney cancer risk following exposure to ionising radiation. Subsequently, Grant et al. observed 790 UTC cases (female n=297, male n=493). Nearly 80 percent of cases were in the bladder; cases were three times more common in men than in women; and incidence increased rapidly over the age of 60 years. In males, the ERR per Gy was 0.64 (95% CI: 0.18, 2.1). For kidney cancer, Grant et al. observed 218 cases (female n=100, male n=118). Incidence was twice as high for males. Cigarette smoking was suggested as a reason for differences in outcome for males. Nevertheless, “despite the strong association of smoking and UTC, ERR estimates for radiation exposure were unchanged with the adjustment for smoking” (Grant et al., 2021, p. 143). They found that smoking cigarettes “appeared to be associated with kidney cancer and increased the risk by about 50% after 50 pack-years of smoking but with wide confidence intervals” (Grant et al., 2021, p. 147). The results indicate a strong association (linear dose-response) between radiation and UTC, but no strong association between radiation and kidney cancer.

Based on the LSS data, bladder cancer is thought to be associated with both low- and high-dose radiation (UNSCEAR, 2008, as cited in Ozasa et al., 2012).

Through their study of kidney cancer among the LSS cohort, Richardson and Hamra (2010) found that “incidence of cancer of the renal pelvis and ureters is positively associated with estimated ionizing radiation dose among members of the Life Span Study” (Richardson & Hamra, 2010, p. 840). The ERR per Sv was 1.65 (90% CI: 0.37, 3.78). They noted that the excess risk was greater for people under the age of 55 years. Roughly 70 percent of the study population were aged between 10 years and 50 years at exposure.

Li et al. (2010) used the LSS data to explore the relationship between first and second primary cancers. Of the 77,752 atomic bomb survivors, 14,048 were diagnosed with a primary cancer of whom 1,088 were diagnosed with a second primary cancer. Li et al. found radiation to be related to both first and second primary bladder cancers and that survivors of bladder cancer as a first primary cancer were at a strong risk of developing a second primary cancer.

EVIDENCE ABOUT NON-CANCER EFFECTS

This section presents the evidence about non-cancer effects, specifically psychological, and other non-cancer effects. Other non-cancer effects include a number of effects: cataract; circulatory diseases; dementia, Alzheimer's, Parkinson's, and motor neuron; thyroid disorders; and kidney disease. Evidence is presented first by the traditional hierarchy of evidence, and second by the date of publication.

Psychological effects

There is considerable evidence that people exposed to ionising radiation experience a range of psychological effects. The literature reviewed reports adverse effects on mental health, in particular PTSD, depression, anxiety, alcohol and tobacco use, and suicide. The literature indicates no effect on cognitive function.

Systematic reviews, literature reviews, and other reviews (n=4)

A systematic review by Terayama et al. (2021) examined the emotional and behavioural consequences for survivors eight years after the 2011 Fukushima nuclear disaster. The authors concluded that Fukushima survivors "suffered issues in risk perception, well-being, stigmatization, and alcohol/tobacco use in the first 8 years after the disaster" (Terayama et al., 2021, p. 30). As well as "an increase in suicides compared with residents in the whole of Japan or affected by the earthquake and tsunami, but not by the nuclear disaster" (Terayama et al., 2021, p. 30).

In a Review Series commissioned by The Lancet, *From Hiroshima and Nagasaki to Fukushima 1,* the authors noted that results from Chernobyl studies show substantial psychological effects: "Prevalence of depression and PSTD is increased two decades after the accident in emergency and recovery workers, and general population studies report increased rates of poor self-rated health, clinical and sub-clinical depression, anxiety, and PTSD" (Bromet, Havenaar & Guey, 2011, and Bromet, 2014, as cited in Kamiya et al., 2015, p. 475).

In a Review Series commissioned by The Lancet, *From Hiroshima and Nagasaki to Fukushima 2,* the authors stated that studies with adults from areas contaminated by Chernobyl found that the "incidence of post-traumatic stress disorder (PTSD) and other mood and anxiety disorders doubled, and people had statistically significantly lower subjective ratings of health" (Bromet, 2012, as cited in Hasegawa et al., 2015, p. 485). The finding led The Chernobyl Forum, held in 2006, to conclude that "adverse effects on mental health were the most serious public health issue after the accident" (Hasegawa et al., 2015, p. 485).

Hasegawa et al. (2015) also presented results from the Fukushima Mental Health Survey:

> *The proportion of adults with a PCL score [Posttraumatic Stress Disorder Checklist] of 44 or more (that is, probable PTSD) was 21.6% in 2011 and 18.3% in 2012, similar to that for rescue and clean-up workers (PCL ≥50 20.1%), and higher than that for residents (PCL ≥44 16%) in lower Manhattan after the World Trade Center attacks on Sept 11, 2001. (Farfel et al., 2008, and Stellman et al., 2008, as cited in Hasegawa et al., 2015, p. 485).*

This result suggests that approximately one in five Fukushima survivors and rescue and clean-up workers reported PTSD symptoms meeting and exceeding the clinical threshold for a probable PTSD diagnosis.

Cohort studies (n=3)

Loganovsky, Perchuk, and Marazziti (2016) investigated brain bioelectric activity (using quantitative electroencephalogram, (qEEG)), and neuropsychological and psychiatric conditions with 196 subjects before and after they worked on converting the Chernobyl power plant into an environmentally safe system. Subjects worked on converting the power plant for between 7 and 42 months, with an average of 20.4 months. At follow-up, the authors found increased frequency of qEEG abnormalities, and mild cognitive disorders in roughly 11 percent of subjects (in particular, decreased verbal learning and short-term verbal memory), but no clinically relevant neuropsychiatric disorders. The authors concluded that "taken together, the disturbances observed may be considered as cognitive symptoms of a chronic fatigue syndrome resulting from the exposure to ionizing radiation" (K. Loganovsky et al., 2016, p. 600).

An assessment of the mental health of 295 male clean-up workers 18 years after they were sent to Chernobyl reported that – compared to 397 geographically matched controls – "significantly more clean-up workers developed mood and anxiety disorders, but not alcoholism or IED [Intermittent Explosive Disorder]. They also had higher rates of suicide ideation and severe headaches" (K. Loganovsky et al., 2008, p. 485). Specifically:

> *Relatively more clean-up workers than controls experienced depression (18.0 % v. 13.1 %) and suicide ideation (9.2 % v. 4.1 %) after the accident. In the year preceding interview, the rates of depression (14.9 % v. 7.1 %), post-traumatic stress disorder (PTSD) (4.1 % v. 1.0 %) and headaches (69.2 % v. 12.4 %) were elevated (K. Loganovsky et al., 2008, p. 481).*

Further, it was found that the level of exposure to ionising radiation was associated with the severity of somatic complaints and PTSD symptoms.

An examination of the effects of radiation exposure on cognitive function among 3,113 adult survivors of Hiroshima and Nagasaki (AHS cohort) found that contrary to expectation based on radiotherapy exposure research, "exposure to atomic bomb radiation had no apparent effect on cognitive function" (Yamada et al., 2002, p. 236). However other factors such as age, sex, city, and years of education did affect cognitive function. Cognitive function was assessed using the Cognitive Abilities Screening Instrument (CASI) to assess 10 domains including attention, short and long-term memory, language, and judgement. The authors also "expected an increase in the incidence of or mortality from stroke among irradiated survivors to be associated with an enhanced decline of cognitive function, but we found no such association" (Yamada et al., 2002, p. 238).

Case control studies (2)

A semi-structured survey administered to Russians who immigrated to Israel in the 1990s found that "both the somatic and mental health of Chernobyl survivors were significantly worse than in other immigrants of the same gender and age; a significant share of reported health problems were probably psychosomatic" (Remennick, 2002, p. 309). More specifically, when compared to other immigrants (200 participants), immigrants from Chernobyl-affected areas (180 participants) reported significantly greater depression (35 percent versus 12 percent self-reported depressive episode/s during the last year), cancer-related anxiety (2.8 versus 0.6 on a five-point index), and somatisation (44 percent versus 21 percent reported one episode of somatisation). Additionally "immigrants from contaminated areas tended to use more health services (both conventional and alternative), but were less satisfied with their quality and providers' attitude" (Remennick, 2002, p. 309).

A conventional electroencephalogram (EEG) study conducted after Chernobyl found that participants who had been exposed to ionising radiation showed distinctive EEG patterns, explained as reflective of inhibition of the cortical-limbic system. Explicitly, the authors concluded:

> *In 3–5 years after irradiation, there were irritated EEG changes with paroxysmal activity shifted to the left frontotemporal region (cortical-limbic overactivation) that were transformed 10–13 years after irradiation toward a low-voltage EEG pattern with excess of fast (beta) and slow (delta) activity together with depression of alpha and theta activity (organic brain damage with inhibition of the cortical-limbic system)" (K. N. Loganovsky & Yuryev, 2001, p. 441).*

Loganovsky and Yuryev stress: "it is very important to note that left frontotemporal-limbic dysfunction is the determining pattern of cerebral disorganization leading to schizophrenia," (Flor-Henry, 1983, as cited in K. N. Loganovsky & Yuryev, 2001, p. 453). They hypothesise that "the left (dominant) hemisphere is more vulnerable in right-handed men to whole-body irradiation than the right" (2001, p. 453).

Qualitative studies (n=1)

A qualitative study collected semi-structured interview data from seven atomic veterans and their families (Murphy et al., 1990). Three veterans participated in atomic testing in the Pacific, three participated in atomic testing in Nevada, and one participated in the Hiroshima clean-up. The authors noted that "exposure to low level ionizing radiation has powerful psychological effects on all members of the family" (Murphy et al., 1990, p. 426). The authors found four recurrent themes: "the invalidation of their experiences by government and other authority figures; family concerns about genetic effects on future generations; family members' desire to protect each other from fears of physical consequences; and desire to leave a record of their experiences to help prevent future suffering" (Murphy et al., 1990, p. 418).

Other non-cancer effects

Several non-cancer effects of exposure to ionising radiation have been described in the reviewed literature. These include diverse findings regarding cataract; statistically significant excess risk of circulatory disease; increased incidence of Parkinson's disease; some evidence that low-dose environmental radiation exposure may be associated with higher-than-expected prevalence of antithyroid antibodies; and a possible association between chronic renal dysfunction and later cardiovascular disease mortality.

Cataract

Systematic reviews, literature reviews and other reviews (n=2)

A review of the effect of ionising radiation and ocular disease (Little et al., 2021) in occupationally exposed groups, found an increased risk of cataract from low-dose radiation (<0.1 Gy or 25 mGy/hour) with a linear dose-response association. The sample included the following occupationally exposed groups: Chernobyl liquidators, US radiologic technologists, and Russian Mayak nuclear workers. There was little evidence of low doses increasing the risk of glaucoma or macular degeneration (Little et al., 2021).

A systematic review explored occupational and environmental exposure to low doses (<1 Sv) of ionising radiation and cataract development (Hammer et al., 2013). Diverse findings were reported from cross-sectional studies:

- Among 10,339 atomic bomb survivors, the relative risk of cataract development was RR_{1Sv} =1.06 (95% CI: 1.01; 1.11) (Yamada et al., 2004, as cited in Hammer et al., 2013). The authors found a significant linear dose-response for cataract.
- For 8,607 Chernobyl clean-up workers from Ukraine, exposed between April 1986 and December 1987, prevalence odds ratio (OR), estimated using logistic regression, was OR_{1Sv} of 1.52 (95% CI: 1.01; 2.00) for stage 1 posterior subcapsular (opacities) (Worgul et al., 2007, as cited in Hammer et al., 2013). The data suggests an association between exposure to ionising radiation and cataract development.
- A cohort study on 35,705 US radiologic technologists exposed to X-rays reported a statistically non-significant ERR per Sv of 1.98 (95% CI: 0.69; 4.65) (Chodick et al., 2008, as cited in Hammer et al., 2013). Hammer et al. note, of this study, that the cataracts were self-diagnosed and therefore subjective.
- For 84 Taiwanese residents of cobalt-contaminated buildings there was an ERR per mSv of 0.16 (95% CI: 0.02; 0.31) for focal lens defects (Chen et al., 2001, as cited in Hammer et al., 2013).

- Three studies that "attempted to estimate a dose threshold underneath which the risk is null" all suggest that the dose threshold is at least much lower than was assumed by the ICRP in 2007, and it may not exist (Hammer et al., 2013, p. 313). Latency between exposure and effect is also uncertain, with estimates ranging from 2-3 years to 50 years or more. A suggested reason for the range in latency period is that this may be inversely dependent on dose (Hall et al.,1999, as cited in Hammer et al., 2013).

Circulatory diseases

Systematic reviews, literature reviews, and other reviews (n=3)

A systematic review of the relationship between low- and moderate-dose ionising radiation exposure and circulatory disease by Little et al. (2021) covered cohort studies of occupationally exposed workers and atomic bomb survivors. The authors noted that "lower dose correlations with circulatory disease are emerging in the Japanese atomic bomb survivors and in some occupationally exposed groups, and are still to some extent controversial" (2021, p. 782). In moderate- (0.1-0.5 Gy) or low-dose (<0.1 Gy) exposed groups, they reported a statistically significant excess risk of circulatory disease, specifically ischemic heart disease and stroke, although with some inconsistency in the evidence and non-linearity in the dose-response relationship. They noted that although lifestyle risk factors (e.g., cigarette smoking and obesity) have not been shown to be confounding factors, they may still confound the radiation dose-response.

A systematic review of epidemiological evidence concerning any association between low doses of ionising radiation (doses below 5 Gy or 5 Sv) and circulatory diseases, such as heart diseases and stroke, was published in 2005 (McGale & Darby, 2005). Of the 27 studies reviewed, exposure was via atomic bombings (n=1), treatment of benign disease (n=6), diagnostic examinations (n=5), and occupational groupings (n=15, includes radiologists, radiation workers). McGale and Darby reported mixed findings among the reviewed studies, with some studies finding an association, (such as Cardis et al., 1995, and Ashmore et al., 1998 as cited in McGale & Darby, 2005), and other studies finding no association (such as Matanoski, 1991, McGeoghegan & Binks, 2000a, 2000b, and 2001 as cited in McGale & Darby, 2005). McGale and Darby observed that many of the studies of monitored radiation workers (n=3) have very low power, having only a very small chance of detecting a true effect, or that the results may be distorted by random or systematic errors. They noted that results from two good quality studies of monitored radiation workers (Cardis et al., 1995, and Ivanov et al., 2001, as cited in McGale & Darby, 2005) return increased risk of circulatory diseases estimates that are well-aligned with estimates from studies with atomic bomb survivors; however they caution:

> *Since these studies are both based entirely on exposures below 0.5 Sv, and information on potential confounding factors is limited in the first and absent in the second, these studies do not provide strong evidence of the existence of any risk (McGale & Darby, 2005, p. 255).*

Six studies reviewed by McGale and Darby, considered to be of the best quality, nonetheless provided widely different degrees of detail, preventing meta-analysis. Among those six papers, a study of 90,284 US radiological technologists (Hauptmann et al., 2003, as cited in McGale

& Darby, 2005), which appropriately adjusted for smoking and other behaviours known to be associated with circulatory diseases, reported "clearly increasing trends in mortality from circulatory disease, and especially from stroke, with measures that were correlated with dose" (2005, p. 255). McGale and Darby concluded that the study by Hauptmann et al. supported the suggestion from the study of atomic bomb survivors that "there is likely to be an effect of radiation on the risks of mortality from heart disease or stroke at doses below 5 Gy or 5 Sv" (McGale & Darby, 2005, p. 255).

In a Review Series commissioned by The Lancet, *From Hiroshima and Nagasaki to Fukushima 1* the authors noted that the risk of cardiovascular disease is increased at high doses (Kamiya et al., 2015).

Cohort studies (n=5)

Mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 workers' confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). The mean dose to the heart was 43.8 mGy, and death from Ischemic Heart Disease (IHD) was significantly below expected with an SMR of 0.80 (95% CI: 0.78, 9.82, n=5,410), and the ERR at 100 mGy was -0.01 (95% CI: -0.06, 0.04). Amongst the sample, 5,410 deaths had been attributed to IHD, and there was no evidence of a radiation association.

Boice et al. (Boice, Cohen, Mumma, Golden, et al., 2022) conducted an extended follow-up mortality study on 15,737 workers at the LANL. They found IHD occurred below population expectation and found no radiation-related association with IHD among 3,043 deaths. The ERR per 100 mGy for IHD was -0.06 (95% CI: -0.16, 0.04). Similarly, they found cerebrovascular disease occurred below population expectation and found "no evidence for a radiation association for cerebrovascular disease, based on 871 confirmed deaths among LANL workers" (Boice, Cohen, Mumma, Golden, et al., 2022, p. 740). The ERR at 100 mGy for cerebrovascular disease was -0.11 (95% CI: -0.35, 0.12).

A prospective study examined the risk of fatal and non-fatal stroke among a sample (all eligible participants with appropriate data were included) of the RERF cohort (n=9,515, 34.8 percent male), who are survivors of the nuclear bombs dropped on Hiroshima and Nagasaki (Takahashi et al., 2012). Strokes among the study population were identified using the International Classification of Disease and the incidence rate for these events was calculated. The study found that the "risk of haemorrhagic stroke increases with rising radiation exposure for both sexes, effects in women are less apparent until doses exceed a threshold at 1.3 Gy" (Takahashi et al., 2012, p. 1). For males the risk rose consistently from 11.6 to 29.1 per 10,000 person-years as doses increased from <0.05 to ≥2 Gy (p=0.009). Also reported was that there was no statistically significant relationship between the risk of ischaemic stroke and radiation exposure for either sex.

A report by Ozasa et al. (2012) provided an overview of cancer and non-cancerous diseases amongst the LSS cohort (n=86,611) over a period of 50 years (from 1950 to 2003). The Report is the 14th in a series and includes information on studies conducted in the six years since the previous report. Regarding non-cancer disease excess risks, they noted the risks "to be significantly elevated for diseases of the …circulatory system (0.11, 95% CI: 0.05, 0.17)" (Ozasa et al., 2012, p. 235).

Data from the LSS cohort was examined to investigate the association between mortality from heart disease and exposure to ionising radiation (Shimizu et al., 2010). The LSS cohort consists of 86,611 survivors of the nuclear bombs dropped at Hiroshima and Nagasaki who received estimated radiation doses between 0 and >3 Gy. In total there were 19,054 deaths from circulatory disease amongst the cohort. The study "found dose-response evidence for risk of heart disease and stroke among atomic bomb survivors over the radiation dose range 0-4 Gy (mostly 0-2 Gy)" (Shimizu et al., 2010, p. 5).

Cross-sectional studies (n=1)

Nakamizo et al. (2021) conducted a cross-sectional study investigating the association between radiation exposure and atherosclerosis in survivors of the nuclear bombs dropped on Hiroshima and Nagasaki. A sample of 3,274 participants recruited to this study from the AHS cohort were examined for 14 clinical-physiological indicators of atherosclerosis and the mean radiation dose was 0.30 Gy. Based on the clinical indicators, three known atherosclerotic pathologies were modelled. The study found statistically significant associations between radiation and calcification and plaque, with no significant associations identified for arterial stiffness.

Dementia, Alzheimer's, Parkinson's, and motor neuron

Cohort studies (n=3)

Boice et al. (Boice, Cohen, Mumma, Golden, et al., 2022) conducted an extended follow-up mortality study on 15,737 workers at the LANL. The authors noted that there was significantly more Parkinson's disease among LANL workers than in the general population, with a SMR of 1.16 (95% CI: 1.00, 1.34) (n=193). "A positive association with radiation was seen, ERR per 100 mGy of 0.16 (95% CI: -0.07, 0.40)" (Boice, Cohen, Mumma, Golden, et al., 2022, p. 741). Further, a dose-response relationship was suggested but not statistically significant. They observed no radiation-related increase for dementia, Alzheimer's disease, or motor neuron disease.

Mortality data from the MPS computed the risks for a range of health outcomes from chronic exposure to radiation amongst 29,076 workers' confirmed and expected deaths (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). Boice et al. found that incidence of dementia, Alzheimer's, Parkinson's, and motor neuron diseases was not increased. Amongst 140 deaths with Parkinson's, they found a nonsignificant dose-response: ERR per 100 mGy of 0.24 (95% CI: -0.02, 0.50), which they noted to be consistent with other studies.

Data from the AHS was examined in a cohort study to investigate whether exposure to nuclear bomb radiation (relatively low dose of ≤4 Gy) was associated with a higher incidence of dementia (Yamada et al., 2009). A sample of 2,286 survivors of the nuclear bombs dropped on Hiroshima and Nagasaki were studied. Participants were grouped by exposure and dementia incidence rates were calculated for each group. Incidence per 1000 person-years was 16.3 for the <5 mGy group, 17.0 for the 5-499 mGy group, and 15.2 for the ≥500 mGy group. This finding indicates that: "radiation exposure was not a risk factor for dementia among atomic bomb survivors exposed after they were 13 years old" (Yamada et al., 2009, p. 13).

Thyroid disorders

Systematic reviews, literature reviews, and other reviews (n=1)

A literature review (Eheman et al., 2003) was designed to explore the plausibility of an association between environmental thyroidal radiation and the presence of antithyroid antibodies as well as autoimmune thyroid disease (hypothyroidism and hyperthyroidism). Eheman et al. reported that a study of a subset of AHS participants (n=2,061) found no significant relationship between radiation dose (estimated whole-body doses ranged between 0 and 5.6 Gy) and either antithyroglobulin antibody or antithyroid-microsomal antibody (Fujiwara et al., 1994, as cited in Eheman et al., 2003).

- Another study described by Eheman et al. (2003) used autopsy data from 5,028 Hiroshima survivors who had died between 1951 and 1985, with an age range of 9 to 100 years (mean age 69.4 years). Thyroid dose estimates ranged between 0 and greater than 1 Gy. Thyroiditis was identified in 50 cases, but “no relationship was observed between radiation dose and chronic thyroiditis” (Howard et al., 1997, as cited in Eheman et al., 2003, p. 457).
- Another study described by Eheman et al. (2003) focused on people (both adults and children) exposed to fallout from above-ground nuclear tests (Castle Bravo) conducted in the Marshall Islands (specifically the Rongelap and Utirik populations). Of the 252 people followed and treated since the 1950s, 14 people (5.6 percent) were diagnosed with hypothyroidism (Cronkite et al., 1995, as cited in Eheman et al., 2003). Eheman et al. are not overt with an interpretation of this finding, but the proportion (5.6 percent) is well aligned with the usual range for this condition, of 5 percent diagnosed and an estimated additional 5 percent being undiagnosed.[57] Additionally, the authors found no increase in autoimmune thyroiditis. Higher radiation exposure was not associated with a difference in results.

Eheman et al. (2003)[58] conclude from their review that there is some evidence indicating that low-dose environmental radiation exposure may be associated with higher than expected prevalence of antithyroid antibodies, which are string predictors of the subsequent development of thyroid dysfunction.

Kidney disease

Cohort studies (n=2)

Boice et al. (Boice, Cohen, Mumma, Golden, et al., 2022) conducted an extended follow-up mortality study on workers at the LANL. The cause of death for 15,737 workers was examined, with data from the 1940s through 2017. They found no increase in non-malignant kidney disorders related to radiation dose among LANL nuclear workers.

An earlier study (Adams et al., 2012) investigated the relationship between radiation, chronic renal dysfunction, and cardiovascular disease. Adams et al. hypothesised that as the kidney is involved in blood pressure regulation, chronic renal dysfunction might explain the

---

57 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6822815/

58 Eheman et al. also reviewed studies that focused on children, which are not included in this review.

relationship between radiation and cardiovascular disease. Subsequently, Adams et al. found a possible association between chronic renal dysfunction and later cardiovascular disease mortality amongst the LSS population. They noted that this association was most evident in people exposed to full-body irradiation prior to the age of 40 years. They concluded:

> *Given the importance of cardiovascular disease as a cause of mortality in those exposed to whole-body radiation and therapeutic radiation to the chest, our results suggest that future studies should seek to better measure kidney function over time and evaluate its association with the incidence and mortality of cardiovascular events, especially myocardial infarction (Adams et al., 2012, p. 8).*

EVIDENCE ABOUT GENETIC EFFECTS

This section presents the evidence about genetic effects, specifically genetic effects for exposed adults, and genetic effects for descendants of exposed adults. Evidence is presented first by the traditional hierarchy of evidence, and second by the date of publication.

Genetic effects for exposed adults

There is mixed evidence about health effects from genetic alterations for adults exposed to ionising radiation. There is some evidence for changes in molecular markers demonstrating DNA damage, and some evidence for genomic changes in mutated genes for people who later developed MDS.

Cohort studies (n=2)

Bazyka et al. (2020) studied 300 staff performing shift professional activities at the Chernobyl Shelter inside the contaminated area of the 30-km Chernobyl exclusion zone. The study focused on the influence of borderline exposure to annual professional limits and age on expression of molecular markers. The study found changes in biomolecular markers demonstrating DNA damage following radiation doses higher than 35 mSv, and a higher susceptibility to exposure in workers younger than 40 years of age. The results are described as statistically significant.

Taguchi et al. (2020) studied samples from 32 adults (14 male) from Nagasaki who were exposed to radiation from the atomic bomb and subsequently developed MDS and had treatment at two hospitals in the Nagasaki region. They compared those who were within 2.7km of the hypocentre to those who were between 2.7km and 10km away for genomic changes. They found significant genomic changes in the profile of mutated genes of those within 2.7km of the hypocentre compared to those who were between 2.7km and 10km away. Some of the mutations identified have been associated with types of leukaemia by other studies.

Genetic effects for descendants

Among 15 reviews and studies included in this review, and despite the reanalysis of data using more robust methods, none have reported statistically significant findings about effects on the descendants of people exposed to ionising radiation.

Systematic reviews, literature reviews, and other reviews (n=5)

In a Review Series commissioned by The Lancet, *From Hiroshima and Nagasaki to Fukushima 1* the authors noted that "risks of hereditary malformations, cancer, or other diseases in children of atomic bomb survivors did not increase detectably with paternal or maternal dose" (Kamiya et al., 2015, p. 469).

A review of studies on a large cohort of Japanese atomic bomb survivors (n=93,741) through the RERF investigated the impact of radiation exposure from the atomic bombs at Hiroshima and Nagasaki at an individual and group level (Cullings, 2014). One study reviewed (Douple et al., 2011, as cited in Cullings, 2014) investigated genetic effects on 77,000 children born between 1948 and 1953 of male and female survivors among RERF studies. As at 2014 (at an attained age of 61 to 66 years) no statistically significant evidence had been identified of any inherited effect (specific outcomes are not stated by Cullings et al.) of parental exposure (Douple et al. 2011 as cited in Cullings, 2014). Further studies on the RERF population identified no evidence of increased cancer incidence or mortality among the children of survivors (Izumi et al. 2003a and 2003b as cited in Cullings, 2014).

A review of the papers on germ cell mutations associated with ionising radiation (Olshan, 1995) concluded that although radiation had induced damage in germ cells in animal experiments, the detection of induced mutations and disease in the children of people exposed to radiation has been limited.

> *The outcomes of more than 76,000 pregnancies of exposed individuals and the health of their children were carefully monitored for an array of health parameters. … The analysis of the atomic bomb data has generally not shown any indication of an increased risk among exposed pregnancies for a variety of outcomes, including stillbirth, congenital defects, low birthweight, malignancies, and cytogenetic abnormalities (Olshan, 1995, p. 76).*

A 1995 review (Little et al., 1995) looked at the risk of children developing leukaemia following parental radiation exposure pre-conception. The concern arose from a 1983 television documentary that proposed a link between cancer cases in young people and the Sellafield nuclear installation in Cumbria, England. The review critically assessed the proposed link, looking at the subsequent studies of preconception radiation exposure and childhood leukaemia, both in the UK and internationally, and animal studies. They concluded that paternal pre-conception exposure did not explain the increased incidence of childhood leukaemia observed near the Sellafield nuclear installation and that although some animal studies have shown a possible link, studies in people have not been able to substantiate this association.

A case-control study (Gardner et al., 1990 and 1992, as cited in Olshan, 1995) investigated excess childhood leukaemia in the region where the Sellafield nuclear processing facility is located. The study focused on 52 cases of leukaemia, 22 cases of NHL, and 23 cases of Hodgkin's lymphoma amongst children diagnosed between 1950 and 1983. Olshan reported that "the major findings included excess risks for leukaemia and NHL for children born near Sellafield and whose fathers were employed at the nuclear reprocessing facility" (Gardener et al., 1990 and 1992, as cited in Olshan, 1995, p. 76). The relative risk estimate was 8.38 (95% CI: 1.35, 51.99) for 10 mSv or more in the six months prior to conception. Olshan noted that the findings remained controversial, largely due to the implied sensitivities to ionising radiation suggested by the results to be 50 times or more greater than what was predicted by the data from the LSS; the absence of other studies showing any association between cancer in the children of nuclear power plant workers; and the lack of any increase in children born with genetic diseases or birth defects in the Sellafield area.

A 1995 review of the delayed effect of external radiation exposure noted that, despite the increasing sophistication of laboratory techniques from 1948 to 1995, no studies had found genetic effects in the children of parents where one or both were atomic bomb survivors (Miller, 1995).

Cohort studies (n=11)

A cohort study examined the presence of germline mutations (a gene change in a reproductive cell that becomes incorporated into the DNA of every cell in the body of the children) in the families (n=30) of UK military personnel (all men) who were identified as nuclear test veterans compared with control families (n=30) (Moorhouse et al., 2022). The main finding of the study was that there were “no significant increases in the frequency of de novo mutations in the offspring to nuclear test veterans fathers” (Moorhouse et al., 2022, p. 4).

A cohort study conducted on the F1 cohort of the LSS cohort (children who had at least one parent who was an atomic bomb survivor) examined the risk of major congenital malformations and perinatal deaths in the children (n=71,603) (Yamada et al., 2021). The study was a reassessment of data used in previous studies (see below) using a more refined radiation dose estimate based on distance and location. The study found no statistically significant associations that indicated children were at a greater risk of major congenital malformation or perinatal death.

A study conducted on the F1 cohort of the LSS cohort (children who had at least one parent who was an atomic bomb survivor) (n=76,814) investigated the incidence of cancer and mortality from common adulthood diseases (such as hypertension, diabetes, stroke, asthma) (Milder et al., 2016). A mail survey was sent to a subset of this cohort and 16,183 completed surveys were returned. No statistically significant associations were identified: “exposure categories seem, at the present, to have little if any correlation with the outcomes discussed in this report” (Milder et al., 2016, p. 1320).

A prospective cohort study drew upon the F1 mortality cohort from the LSS to examine mortality risk among singleton children (n=75,327) born in Hiroshima and Nagasaki whose parents (one or both) were survivors of the nuclear bombs dropped in each city (Grant et al., 2015). These children were matched to children born at least 2.5km outside of these cities in Japan. The median follow-up period was 54.3 years during which 6,567 participants died. The study found no statistically significant associations between cancer and non-cancer mortality risk and parental radiation exposure.

A cohort study of the children of male and female survivors (n=11,951) of the nuclear bombs at Hiroshima and Nagasaki examined the adult onset of diabetes mellitus, hypercholesterolemia, hypertension, myocardial infarction, angina pectoris, and stroke (Fujiwara et al., 2008). The study did not find any evidence of association between the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, IHD, and stroke in children of those with radiation exposure.

A cohort study examined the presence of hereditary minisatellite mutations among 155 descendants of male Estonian clean-up workers at Chernobyl (Kiuru et al., 2003). Blood samples of children born to clean-up workers either pre or post the Chernobyl accident were collected and examined for the presence of confirmed minisatellite mutations. The study found that children born after the Chernobyl disaster had a slightly higher number of mutations, but these findings were not statistically significant.

A cohort study investigated the presence of inherited mutant alleles in children (n=183) born to male Chernobyl clean-up workers (n=161) compared to children (n=163) from families (n=163) living in non-irradiated areas of Ukraine (Livshits et al., 2001). DNA samples were extracted from the blood collected from the fathers and children of each family and compared. The study found no statistically significant difference between the presence of mutated alleles in the children between the exposed and control groups.

A cohort study examined whether children (n=39,557) born to parents (roughly 80 percent fathers) who have occupational exposure to ionising radiation are at an increased risk of developing leukaemia or cancers prior to their 25th birthday (Roman et al., 1999). The observed number of cases of leukaemia in the exposed population were similar to the expected number of cases based on national rates for England and Wales. The standardised incidence ratios calculated were all close to 100, indicating there was no statistically significant difference.

A retrospective birth cohort study investigated the association between the prevalence of childhood leukaemia in the children born between 1950 and 1989 (n=10,363) to fathers who worked at the Sellafield nuclear installation in Seascale (Parker et al., 1993). The study considered the dose of whole-body ionising radiation received by fathers in their total time working at Sellafield and in the six months prior to conception of their children. The main finding of the study is that: “the distribution of the paternal preconceptional radiation dose is statistically incompatible with the exposure providing a causal explanation for the cluster of childhood leukaemia in Seascale” (Parker et al., 1993, p. 966).

The possibility of genetic effects on the children of atomic bomb survivors was explored early in the work of the ABCC, (Neel and Schull, 1991, as cited in Cullings, 2014) including 77,000 pregnancies among parents exposed to ionising radiation. The study found no significant effects. Cullings et al. report that this study was been repeated several times, using more developed methodologies, “but with no statistically significant results to date” (Douple et al., 2011, as cited in Cullings, 2014, p. 290). “Neither cancer incidence (Izumi et al., 2003a) nor mortality (Izumi et al., 203b) among the children has shown an effect of parental exposure” (Cullings, 2014, p. 290).

Otake et al. (1990) conducted an analysis of parental exposure (50 percent fathers) to radiation and the association with adverse pregnancy outcomes between 1948 and 1953 (children conceived, on average, about five years after the bombings) in the children of survivors of the nuclear bombing of Hiroshima and Nagasaki. The outcomes of interest included stillborn children and major congenital anomaly. The analysis did not find a statistically significant effect of combined parental exposure, but did find that the risk for stillbirth and major congenital anomaly increased with increasing dose, decreased with paternal age, and increased with maternal age.

Descriptive studies (n=1)

A descriptive study investigated whether de novo variants (mutation/alteration in the genome of any organism that was not present or transmitted by their parents) occurred in the children (n=2,229) of fathers who were nuclear bomb survivors from Hiroshima and Nagasaki (Horai et al., 2018). The results of the study found no gross structural variants and no significant genetics effects in the children of the sampled of survivors.

EVIDENCE BY EVENT

This review has focused on health effects from exposure to ionising radiation, as experienced by men, mainly through eight nuclear events. Below, the findings described in the section above are summarised and presented by nuclear event. Some events considered together in the literature are grouped for the presentation of evidence below, specifically: Hiroshima and Nagasaki, Marshall Islands and Three Mile Island, Operation Grapple, Sellafield/Windscale Fire, Chernobyl, and Fukushima. This section concludes with a table that summarises the associations (no association, uncertain association, and association) between these events and health effects.

Hiroshima and Nagasaki

Hiroshima and Nagasaki are largely considered together in the literature, with the RERF/ABCC LSS, AHS, and F1 being the associated longitudinal studies with over 50 years of follow-up.

Exposure to atomic bomb radiation increases the risk of cancer throughout the life of the exposed person (Preston et al., 2003, as cited in Ozasa et al., 2012).

- Statistically significant associations have been identified for prostate cancer (Mabuchi et al., 2021, as cited in Ruhm et al., 2022); bladder cancer, at both high- and low-dose radiation, and especially in men over 60 years of age (Grant et al., 2021; UNSCEAR, 2008, as cited in Ozasa et al., 2012); kidney cancer, particularly in the renal pelvis and ureters, but some of these results were confounded by cigarette smoking (Grant et al., 2021; Richardson & Hamra, 2010); AML (Hsu et al., 2013, as cited in Ruhm et al., 2022); and calcification and plaque in the circulatory system (Nakamizo et al., 2021).

- There is some evidence that low-dose environmental radiation may be associated with higher than expected prevalence of antithyroid antibodies, which are strong predictors of thyroid dysfunction (Eheman et al., 2003); there is uncertainty about the dose-response for tumours of the central nervous system (Brenner et al., 2020, as cited in Ruhm et al., 2022); there are mixed findings concerning colorectal cancers (Bockwoldt et al., 2021; Sugiyama et al., 2020, as cited in Ruhm et al., 2022); there are contested diagnoses for liver cancer (French et al., 2020); and complex dose-response relationships have been observed for lung cancer, with heavy smokers seeming to have a lower ERR than low to moderate smokers (Cahoon et al., 2017, as cited in Ruhm et al., 2022).

- There is no evidence of a statistically significant association between parental exposure to ionising radiation and any inherited effect for descendants (Douple et al., 2011, Izumi et al., 2003a and 2003b, Neel and Schull, 1991, as cited in Cullings, 2014; Grant et al., 2015; Milder et al., 2016; Yamada et al., 2021). There is no statistical significance for stroke (Takahashi et al., 2012); there is no association with biliary tract cancer (Sadakane et al., 2019, as cited in Ruhm et al., 2022); stroke (Yamada et al., 2002); arterial stiffness (Nakamizo et al., 2021); or dementia (Yamada et al., 2009).

Marshall Islands and Three Mile Island

Data about atomic veterans from the nuclear testing in the Marshall Islands, and nuclear workers at Three Mile Island, are included in the MPS.

Through the MPS data, a dose-response relationship between chronic exposure to radiation and Parkinson's disease was suggested but non-significant (Boice, Cohen, Mumma, Hagemeyer, et al., 2022). An association was also found with leukaemia, with Boice et al. commenting that those who had experienced acute exposure were at higher risk than those who experienced prolonged exposure; and they found a suggestion of a dose-response in relation to oesophageal cancer.

Although lung cancer was found to be significantly elevated in an MPS cohort, Boice et al. commented that workers were also exposed to asbestos and had high rates of cigarette smoking, potentially confounding the results (Boice, Cohen, Mumma, Hagemeyer, et al., 2022).

No association was found amongst the MPS cohort and MDS, nor MDS in combination with AML; solid cancers (as a group); prostate cancer; or IHD (Boice, Cohen, Mumma, Hagemeyer, et al., 2022).

Operation Grapple

A study of exposed Royal New Zealand Navy personnel (Pearce et al., 1990, as cited in Yousif et al., 2010) found no increase in testicular cancer incidence or mortality. No other outcomes were identified.

Sellafield/Windscale Fire

The reviewed literature relating to Sellafield shows a significantly raised ERR for lung cancer (Gillies et al., 2017, as cited in Ruhm et al., 2022); and a significant risk of leukaemia other than CLL (Gillies et al., 2019, at cited in Boice, Cohen, Mumma, Golden, et al., 2022; IARC Study Group on Cancer Risk among Nuclear Industry Workers, 1994).

There are contested findings about excess risk of leukaemia amongst children fathered by Sellafield workers (Little et al., 1995; Olshan, 1995; Parker et al., 1993); and the reason for excess stroke amongst Sellafield plutonium workers remains unclear (McGale & Darby, 2005).

Chernobyl

Adults from contaminated areas have been found to have statistically significantly lower subjective ratings of health; doubled incidence of post-traumatic stress disorder and other mood and anxiety disorders (Hasegawa et al., 2015); and to be significantly more at risk of cataract (Worgul et al., 2007, as cited in Hammer et al., 2013).

Associations have been found between exposure to ionising radiation and chronic fatigue syndrome (K. Loganovsky et al., 2016); mood and anxiety disorders, severe headache, and suicidal ideation (K. Loganovsky et al., 2008); significantly greater depression, cancer-related anxiety, and somatisation amongst Chernobyl survivors compared to other new immigrants to Israel (Remennick, 2002); and an EEG study with Chernobyl survivors found evidence of changes to the frontotemporal region, indicative of cerebral disorganisation that leads to schizophrenia (Flor-Henry, 1983, as cited in K. N. Loganovsky & Yuryev, 2001). An association has been found for solid cancer incidence (Ivanov et al., 2020, Cologne et al., 2018, as cited in Ruhm et al., 2022); and for thyroid cancer, noting that this association was stronger for people exposed prior to age 30 (Smailyte et al., 2021, as cited in Ruhm et al., 2022).

Children born to male Estonian clean-up workers after the Chernobyl accident were found to have a slightly higher number of genetic mutations, but these findings were not statistically or clinically significant (Kiuru et al., 2003).

Studies exploring the risk of leukaemia and NHL amongst Chernobyl liquidators (Kesminiene et al., 2008, as cited in Ruhm et al., 2022) have been described by Ruhm et al. as “difficult to interpret” due to large confidence intervals (Ruhm et al., 2022, p. 9).

Fukushima

To date, mental health has been found to be negatively impacted for survivors of the Fukushima event, with risk perception issues, reduced wellbeing, stigmatisation, increased alcohol and tobacco use, and increased suicide (Terayama et al., 2021). The Fukushima Mental Health Survey showed that the proportion of adults with probable post-traumatic stress disorder was 21.6 percent in 2011 and 18.3 percent in 2012 (Farfel et al., 2008, and Stellman et al., 2008, as cited in Hasegawa et al., 2015).

Summary of the associations between events and health effects

No association
Uncertain association
Association

	Hiroshima and Nagasaki	Marshall Islands and Three Mile Island	Operation Grapple	Sellafield/Windscale Fire	Chernobyl	Fukushima
Leukaemia, lymphoma, multiple myeloma	Linear dose effect, stronger for acute myeloid leukaemia Significant dose-response for leukaemia	SMR of 1.06	–	Significant risk of leukaemia	ERR of 5.0 per Gy for leukaemia (contested)	–
Solid cancer	Increased risk of cancer mortality throughout life	Little evidence of a dose-response relationship	–	–	Mortality raised at 0.48	Dose-response relationship, but unclear at low doses
Bone cancer	–	–	–	–	–	–
Central nervous system cancers	Dose-response for some tumour types	–	–	–	–	–

	Hiroshima and Nagasaki	Marshall Islands and Three Mile Island	Operation Grapple	Sellafield/Windscale Fire	Chernobyl	Fukushima
Colorectal cancer	Significant dose-response for colon cancer Non-significant dose-response for rectal cancer	–	–	–	–	–
Oesophageal cancer	–	Suggested dose-response	–	–	–	–
Liver, biliary tract and pancreatic cancers	Significantly elevated ERR per Gy for liver cancer	–	–	–	–	–
Lung cancer	Complex dose-response, with smoking as a confounder	Significantly elevated mortality	–	ERR significantly raised at doses of 300-400 mGy (for mortality and incidence)	–	–
Prostate cancer	Significant linear dose-response	No elevated mortality	–	–	–	–
Testicular cancer	–	–	No increase in incidence or mortality	–	–	–
Thyroid cancer	–	–	–	–	Statistically significant standardised	–

	Hiroshima and Nagasaki	Marshall Islands and Three Mile Island	Operation Grapple	Sellafield/Windscale Fire	Chernobyl	Fukushima
					incidence ratio of 3.13 (contested)	
Urinary tract cancers	UTC and kidney cancer incidence higher for men, possibly confounded by smoking	–	–	–	–	–
Psychological effects	No apparent effect on cognitive function Psychological effects found in qualitative study	–	–	–	Adverse effects on mental health (PTSD, depression, anxiety)	Adverse effects on mental health (suicide, alcohol/tobacco use, PTSD)
Cataract	–	–	–	–	Little evidence of low dose increasing risk	–
Circulatory diseases	Significantly elevated risk	No evidence of association between radiation and IHD	–	–	–	Risk of CVD is increased
Dementia, Alzheimer's, Parkinson's, motor neuron	Not a risk factor for dementia (when exposed after 13 years of age)	Non-significant dose-response for Parkinson's disease	–	–	–	–

	Hiroshima and Nagasaki	Marshall Islands and Three Mile Island	Operation Grapple	Sellafield/Windscale Fire	Chernobyl	Fukushima
Thyroid disorders	No relationship observed	No relationship observed	–	–	–	–
Kidney disease	Possible association between chronic renal dysfunction and CVD among full body irradiated people aged <40 years	–	–	–	–	–
Genetic effects for adults	Genomic changes in mutated genes for people who later developed MDS	–	–	–	Changes in biomolecular markers observed after doses >35 mSv	–
Genetic effects for descendants	No statistically significant associations	–	–	No substantiated association (controversial)	No statistically significant findings	No detectable increase in hereditary malformations, cancer or other diseases

CONCLUSION

This review of the literature has shown that exposure to ionising radiation is more likely to be associated with some cancers than with others. There appears to be more and stronger evidence of an association between exposure to ionising radiation and leukaemia, lymphoma, and multiple myeloma than for other disease conditions. Nevertheless, even with leukaemia there are mixed results, in part because so much depends on the exposure dose, whether exposure was acute or prolonged, the age at exposure, and the length of time since exposure. Over time, the focus of researchers has moved from demonstrating associations, to estimating dose-response rates, and more recently still, the literature relating to Chernobyl and Fukushima has moved beyond cancers and other physical disease conditions to consider the psychological effects. Concerns about inherited effects have been more constant, with more advanced methods used to explore historical data only to return the same result: no association between parental exposure to ionising radiation and genetic markers or birth defects in children is apparent.

Six of the articles referenced in this review were published in 2022. This most recent literature has concluded that low doses of prolonged exposure to ionising radiation are a matter for concern (Ruhm et al., 2022); that exposure dose matters, (Otani et al., 2022); and that there is no evidence of increased germline mutations (Moorhouse et al., 2022). However, the conclusions are not always consistent. Two studies lead by Boice, both published in 2022, reached different conclusions about increased risk of leukaemia across two different populations of nuclear workers. The data from the MPS nuclear power plant workers cohort shows an increased risk following prolonged exposure to ionising radiation (Boice, Cohen, Mumma, Hagemeyer, et al., 2022), but the LANL data shows there to be little evidence of increased risk for leukaemia (Boice, Cohen, Mumma, Golden, et al., 2022). Adding to the inconsistencies around the association with leukaemia, a reanalysis of LSS data found a significant dose-response (Fujihara et al., 2022). The authors of these studies all consider that more research is necessary.

REFERENCES

Adams, M. J., Grant, E. J., Kodama, K., Shimizu, Y., Kasagi, F., Suyama, A., Sakata, R., & Akahoshi, M. (2012). Radiation dose associated with renal failure mortality: A potential pathway to partially explain increased cardiovascular disease mortality observed after whole-body irradiation. *Radiation Research*, *177*(2), 220–228. Scopus. https://doi.org/10.1667/RR2746.1

Alexis-Martin, B., Bolton, M. B., Hawkins, D., Tisch, S., & Mangioni, T. L. (2021). Addressing the Humanitarian and Environmental Consequences of Atmospheric Nuclear Weapon Tests: A Case Study of UK and US Test Programs at Kiritimati (Christmas) and Malden Islands, Republic of Kiribati. *Global Policy*, *12*(1), 106–121. https://doi.org/10.1111/1758-5899.12913

Bazyka, D., Ilienko, I., Golyarnik, N., Belyaev, O., & Lyaskivska, O. (2020). Gene Expression and Cellular Markers of Occupational Radiation Exposure in Chernobyl Shelter Construction Workers. *Health Physics*, *119*(1), 37–43. Scopus. https://doi.org/10.1097/HP.0000000000001277

Bockwoldt, B., Sugiyama, H., Tsai, K., Bhatti, P., Brenner, A. V., Hu, A., Kerr, K. F., Morenz, E., French, B., & Phipps, A. I. (2021). Gastrointestinal cancer survival and radiation exposure among atomic bomb survivors: The life span study. *Cancer Epidemiology Biomarkers and Prevention*, *30*(2), 412–418. Scopus. https://doi.org/10.1158/1055-9965.EPI-20-1239

Boice, J. D., Cohen, S. S., Mumma, M. T., Hagemeyer, D. A., Chen, H., Golden, A. P., Yoder, R. C., & Dauer, L. T. (2022). Mortality from leukemia, cancer and heart disease among U.S. nuclear power plant workers, 1957-2011. *International Journal of Radiation Biology*, *98*(4), 657–678. https://doi.org/10.1080/09553002.2021.1967507

Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., & Ellis, E. D. (2022). The Million Person Study, whence it came and why. *International Journal of Radiation Biology*, *98*(4), 537–550. https://doi.org/10.1080/09553002.2019.1589015

Boice, J. D., Jr., Cohen, S. S., Mumma, M. T., Golden, A. P., Howard, S. C., Girardi, D. J., Ellis, E. D., Bellamy, M. B., Dauer, L. T., Samuels, C., Eckerman, K. F., & Leggett, R. W. (2022). Mortality among workers at the Los Alamos National Laboratory, 1943-2017. *Int J Radiat Biol*, *98*(4), 722–749. https://doi.org/10.1080/09553002.2021.1917784

Cullings, H. M. (2014). Impact on the Japanese atomic bomb survivors of radiation received from the bombs. *Health Physics*, *106*(2), 281–293. Scopus. https://doi.org/10.1097/HP.0000000000000009

Daniels, R. D., Schubauer-Berigan, M. K., Daniels, R. D., & Schubauer-Berigan, M. K. (2011). A meta-analysis of leukaemia risk from protracted exposure to low-dose gamma radiation. *Occupational & Environmental Medicine*, *68*(6), 457–464. CINAHL with Full Text. https://doi.org/10.1136/oem.2009.054684

Eheman, C. R., Garbe, P., & Tuttle, R. M. (2003). Autoimmune thyroid disease associated with environmental thyroidal irradiation. *Thyroid*, *13*(5), 453–464. Scopus. https://doi.org/10.1089/105072503322021115

French, B., Sadakane, A., Cologne, J., Mabuchi, K., Ozasa, K., & Preston, D. L. (2020). Misclassification of primary liver cancer in the Life Span Study of atomic bomb survivors. *Int J Cancer*, *147*(5), 1294–1299. https://doi.org/10.1002/ijc.32887

Fujihara, M., Sakata, R., Yoshida, N., Ozasa, K., Preston, D. L., & Mabuchi, K. (2022). Incidence of lymphoid neoplasms among atomic bomb survivors by histological subtype, 1950 to 1994. *Blood*, *139*(2), 217–227. Scopus. https://doi.org/10.1182/blood.2020010475

Fujimura, K., Sugiyama, A., Akita, T., Ohisa, M., Nagashima, S., Katayama, K., Maeda, R., & Tanaka, J. (2021). Screening for M-proteinemia consisting of monoclonal gammopathy of undetermined significance and multiple myeloma for 30 years among atomic bomb survivors in Hiroshima. *International Journal of Hematology*, *113*(4), 576–585. Scopus. https://doi.org/10.1007/s12185-020-03045-y

Fujiwara, S., Suyama, A., Cologne, J. B., Akahoshi, M., Yamada, M., Suzuki, G., Koyama, K., Takahashi, N., Kasagi, F., Grant, E. J., Lagarde, F., Hsu, W. L., Furukawa, K., Ohishi, W., Tatsukawa, Y., Neriishi, K., Takahashi, A. I., Ashizawa, K., Hida, A., … Shore, R. E. (2008). Prevalence of adult-onset multifactorial disease among offspring of atomic bomb survivors. *Radiation Research*, *170*(4), 451–457. Scopus. https://doi.org/10.1667/RR1392.1

Grant, E. J., Furukawa, K., Sakata, R., Sugiyama, H., Sadakane, A., Takahashi, I., Utada, M., Shimizu, Y., & Ozasa, K. (2015). Risk of death among children of atomic bomb survivors after 62 years of follow-up: A cohort study. *Lancet Oncology*, *16*(13), 1316–1323. Scopus. https://doi.org/10.1016/S1470-2045(15)00209-0

Grant, E. J., Yamamura, M., Brenner, A. V., Preston, D. L., Utada, M., Sugiyama, H., Sakata, R., Mabuchi, K., & Ozasa, K. (2021). Radiation risks for the incidence of kidney, bladder and other urinary tract cancers: 1958-2009. *Radiation Research*, *195*(2), 140–148. Scopus. https://doi.org/10.1667/RADE-20-00158.1

Hammer, G. P., Scheidemann-Wesp, U., Samkange-Zeeb, F., Wicke, H., Neriishi, K., & Blettner, M. (2013). Occupational exposure to low doses of ionizing radiation and cataract development: A systematic literature review and perspectives on future studies. *Radiation and Environmental Biophysics*, *52*(3), 303–319. Scopus. https://doi.org/10.1007/s00411-013-0477-6

Hasegawa, A., Tanigawa, K., Ohtsuru, A., Yabe, H., Maeda, M., Shigemura, J., Ohira, T., Tominaga, T., Akashi, M., Hirohashi, N., Ishikawa, T., Kamiya, K., Shibuya, K., Yamashita, S., & Chhem, R. K. (2015). Health effects of radiation and other health problems in the aftermath of nuclear accidents, with an emphasis on Fukushima. *Lancet*, *386*(9992), 479–488. Scopus. https://doi.org/10.1016/S0140-6736(15)61106-0

Hauptmann, M., Daniels, R. D., Cardis, E., Cullings, H. M., Kendall, G., Laurier, D., Linet, M. S., Little, M. P., Lubin, J. H., Preston, D. L., Richardson, D. B., Stram, D. O., Thierry-Chef, I., Schubauer-Berigan, M. K., Gilbert, E. S., & de Gonzalez, A. B. (2020). Epidemiological studies of low-dose ionizing radiation and cancer: Summary bias assessment and meta-analysis. *Journal of the National Cancer Institute - Monographs*, *2020*(56), 188–200. https://doi.org/10.1093/JNCIMONOGRAPHS/LGAA010

Hayashi, T., Furukawa, K., Morishita, Y., Hayashi, I., Kato, N., Yoshida, K., Kusunoki, Y., Kyoizumi, S., & Ohishi, W. (2021). Intracellular reactive oxygen species level in blood cells of atomic bomb survivors is increased due to aging and radiation exposure. *Free Radical Biology and Medicine*, *171*, 126–134. Scopus. https://doi.org/10.1016/j.freeradbiomed.2021.05.017

Horai, M., Mishima, H., Hayashida, C., Kinoshita, A., Nakane, Y., Matsuo, T., Tsuruda, K., Yanagihara, K., Sato, S., Imanishi, D., Imaizumi, Y., Hata, T., Miyazaki, Y., & Yoshiura, K. I. (2018). Detection of de novo single nucleotide variants in offspring of atomic-bomb survivors close to the hypocenter by whole-genome sequencing. *Journal of Human Genetics*, *63*(3), 357–363. Scopus. https://doi.org/10.1038/s10038-017-0392-9

IARC Study Group on Cancer Risk among Nuclear Industry Workers. (1994). Direct estimates of cancer mortality due to low doses of ionising radiation: An international study. *Lancet*, *344*(8929), 1039–1043. Scopus. https://doi.org/10.1016/S0140-6736(94)91706-X

Iwanaga, M., Hsu, W. L., Soda, M., Takasaki, Y., Tawara, M., Joh, T., Amenomori, T., Yamamura, M., Yoshida, Y., Koba, T., Miyazaki, Y., Matsuo, T., Preston, D. L., Suyama, A., Kodama, K., & Tomonaga, M. (2011). Risk of myelodysplastic syndromes in people exposed to ionizing radiation: A retrospective cohort study of Nagasaki atomic bomb survivors. *Journal of Clinical Oncology*, *29*(4), 428–434. Scopus. https://doi.org/10.1200/JCO.2010.31.3080

Kamiya, K., Ozasa, K., Akiba, S., Niwa, O., Kodama, K., Takamura, N., Zaharieva, E. K., Kimura, Y., & Wakeford, R. (2015). Long-term effects of radiation exposure on health. *Lancet*, *386*(9992), 469–478. Scopus. https://doi.org/10.1016/S0140-6736(15)61167-9

Kiuru, A., Auvinen, A., Luokkamäki, M., Makkonen, K., Veidebaum, T., Tekkel, M., Rahu, M., Hakulinen, T., Servomaa, K., Rytömaa, T., & Mustonen, R. (2003). Hereditary minisatellite mutations among the offspring of Estonian Chernobyl cleanup workers. *Radiation Research*, *159*(5), 651–655. Scopus. https://doi.org/10.1667/0033-7587(2003)159[0651:HMMATO]2.0.CO;2

Leuraud, K., Richardson, D. B., Cardis, E., Daniels, R. D., Gillies, M., O'Hagan, J. A., Hamra, G. B., Haylock, R., Laurier, D., Moissonnier, M., Schubauer-Berigan, M. K., Thierry-Chef, I., & Kesminiene, A. (2015). Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): An international cohort study. *The Lancet Haematology*, *2*(7), e276–e281. Scopus. https://doi.org/10.1016/S2352-3026(15)00094-0

Li, C. I., Nishi, N., McDougall, J. A., Semmens, E. O., Sugiyama, H., Soda, M., Sakata, R., Hayashi, M., Kasagi, F., Suyama, A., Mabuchi, K., Davis, S., Kodama, K., & Kopecky, K. J. (2010). Relationship between radiation exposure and risk of second primary cancers among atomic bomb survivors. *Cancer Research*, *70*(18), 7187–7198. Scopus. https://doi.org/10.1158/0008-5472.CAN-10-0276

Little, M. P., Azizova, T. V., & Hamada, N. (2021). Low- and moderate-dose non-cancer effects of ionizing radiation in directly exposed individuals, especially circulatory and ocular diseases: A review of the epidemiology. *International Journal of Radiation Biology*, *97*(6), 782–803. Scopus. https://doi.org/10.1080/09553002.2021.1876955

Little, M. P., Charles, M. W., & Wakeford, R. (1995). A review of the risks of leukemia in relation to parental pre-conception exposure to radiation. *Health Physics*, *68*(3), 299–310. Scopus. https://doi.org/10.1097/00004032-199503000-00001

Livshits, L. A., Malyarchuk, S. G., Lukyanova, E. M., Antipkin, Y. G., Arabskaya, L. P., Kravchenko, S. A., Matsuka, G. H., Petit, E., Giraudeau, F., Gourmelon, P., Vergnaud, G., & Le Guen, B. (2001). Children of Chernobyl cleanup workers do not show elevated rates of mutations in minisatellite alleles. *Radiation Research*, *155*(1), 74–80. Scopus. https://doi.org/10.1667/0033-7587(2001)155[0074:COCCWD]2.0.CO;2

Loganovsky, K., Havenaar, J. M., Tintle, N. L., Guey, L. T., Kotov, R., & Bromet, E. J. (2008). The mental health of clean-up workers 18 years after the Chernobyl accident. *Psychological Medicine*, *38*(4), 481–488. APA PsycInfo. https://doi.org/10.1017/S0033291707002371

Loganovsky, K. N., & Yuryev, K. L. (2001). EEG patterns in persons exposed to ionizing radiation as a result of the Chernobyl accident: Part 1: Conventional EEG analysis. *Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(4), 441–458. Scopus. https://doi.org/10.1176/jnp.13.4.441

Loganovsky, K., Perchuk, I., & Marazziti, D. (2016). Workers on transformation of the shelter object of the Chernobyl nuclear power plant into an ecologically-safe system show qEEG abnormalities and cognitive dysfunctions: A follow-up study. *The World Journal of Biological Psychiatry*, *17*(8), 600–607. APA PsycInfo.

McGale, P., & Darby, S. C. (2005). Low doses of ionizing radiation and circulatory diseases: A systematic review of the published epidemiological evidence. *Radiation Research*, *163*(3), 247–257. Scopus. https://doi.org/10.1667/RR3314

Milder, C., Sakata, R., Sugiyama, H., Sadakane, A., Utada, M., Cordova, K., Hida, A., Ohishi, W., Ozasa, K., & Grant, E. (2016). Initial Report for the Radiation Effects Research Foundation F1 Mail Survey. *Asian Pacific Journal of Cancer Prevention : APJCP*, *17*(3), 1313–1323.

Miller, R. W. (1995). Delayed effects of external radiation exposure: A brief history. *Radiation Research*, *144*(2), 160–169. Scopus. https://doi.org/10.2307/3579255

Moorhouse, A. J., Scholze, M., Sylvius, N., Gillham, C., Rake, C., Peto, J., Anderson, R., & Dubrova, Y. E. (2022). No evidence of increased mutations in the germline of a group of British nuclear test veterans. *Scientific Reports*, *12*(1). Scopus. https://doi.org/10.1038/s41598-022-14999-w

Murphy, B. C., Ellis, P., & Greenberg, S. (1990). Atomic veterans and their families: Responses to radiation exposure. *American Journal of Orthopsychiatry*, *60*(3), 418–427. Scopus. https://doi.org/10.1037/h0079182

Nakamizo, T., Cologne, J., Cordova, K., Yamada, M., Takahashi, T., Misumi, M., Fujiwara, S., Matsumoto, M., Kihara, Y., Hida, A., & Ohishi, W. (2021). Radiation effects on atherosclerosis in atomic bomb survivors: A cross-sectional study using structural equation modeling. *European Journal of Epidemiology*, *36*(4), 401–414. https://doi.org/10.1007/s10654-021-00731-x

Olshan, A. F. (1995). Lessons learned from epidemiologic studies of environmental exposure and genetic disease. *Environmental and Molecular Mutagenesis*, *25*(2 S), 74–80. Scopus. https://doi.org/10.1002/em.2850250611

Otake, M., Schull, W. J., & Neel, J. V. (1990). Congenital malformations, stillbirths, and early mortality among the children of atomic bomb survivors: A reanalysis. *Radiation Research*, *122*(1), 1–11. Scopus. https://doi.org/10.2307/3577576

Otani, K., Ohtaki, M., & Yasuda, H. (2022). Solid cancer mortality risk among a cohort of Hiroshima early entrants after the atomic bombing, 1970-2010: Implications regarding health effects of residual radiation. *Journal of Radiation Research*, *63*(1 Supplement), i45–i53. https://doi.org/10.1093/jrr/rrac036

Ozasa, K., Shimizu, Y., Suyama, A., Kasagi, F., Soda, M., Grant, E. J., Sakata, R., Sugiyama, H., & Kodama, K. (2012). Studies of the mortality of atomic bomb survivors, report 14, 1950-2003: An overview of cancer and noncancer diseases. *Radiation Research*, *177*(3), 229–243. Scopus. https://doi.org/10.1667/RR2629.1

Parker, L., Craft, A. W., Smith, J., Dickinson, H., Wakeford, R., Binks, K., McElvenny, D., Scott, L., & Slovak, A. (1993). Geographical distribution of preconceptional radiation doses to fathers employed at the Sellafield nuclear installation, West Cumbria. *British Medical Journal*, *307*(6910), 966–971. Scopus. https://doi.org/10.1136/bmj.307.6910.966

Remennick, L. I. (2002). Immigrants from Chernobyl-affected areas in Israel: The link between health and social adjustment. *Social Science and Medicine*, *54*(2), 309–317. Scopus. https://doi.org/10.1016/S0277-9536(01)00030-2

Richardson, D. B., & Hamra, G. (2010). Ionizing radiation and kidney cancer among Japanese atomic bomb survivors. *Radiation Research*, *173*(6), 837–842. Scopus. https://doi.org/10.1667/RR2096.1

Roman, E., Doyle, P., Maconochie, N., Davies, G., Smith, P. G., & Beral, V. (1999). Cancer in children of nuclear industry employees: Report on children aged under 25 years from nuclear industry family study. *British Medical Journal*, *318*(7196), 1443–1450. Scopus. https://doi.org/10.1136/bmj.318.7196.1443

Ron, E. (1998). Ionizing radiation and cancer risk: Evidence from epidemiology. *Radiation Research*, *150*(5 SUPPL.), S30–S41. Scopus. https://doi.org/10.2307/3579806

Ron, E. (2007). Thyroid cancer incidence among people living in areas contaminated by radiation from the chernobyl accident. *Health Physics*, *93*(5), 502–511. Scopus. https://doi.org/10.1097/01.HP.0000279018.93081.29

Ruhm, W., Laurier, D., & Wakeford, R. (2022). Cancer risk following low doses of ionising radiation—Current epidemiological evidence and implications for radiological protection. *Mutation Research - Genetic Toxicology and Environmental Mutagenesis*, *873*, 503436. https://doi.org/10.1016/j.mrgentox.2021.503436

Semmens, E. O., Kopecky, K. J., Grant, E., Mathes, R. W., Nishi, N., Sugiyama, H., Moriwaki, H., Sakata, R., Soda, M., Kasagi, F., Yamada, M., Fujiwara, S., Akahoshi, M., Davis, S., Kodama, K., & Li, C. I. (2013). Relationship between anthropometric factors, radiation exposure, and colon cancer incidence in the Life Span Study cohort of atomic bomb survivors. *Cancer Causes and Control*, *24*(1), 27–37. Scopus. https://doi.org/10.1007/s10552-012-0086-8

Shimizu, Y., Kodama, K., Nishi, N., Kasagi, F., Suyama, A., Soda, M., Grant, E. J., Sugiyama, H., Sakata, R., Moriwaki, H., Hayashi, M., Konda, M., & Shore, R. E. (2010). Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *BMJ (Online)*, *340*(7739), 193. Scopus. https://doi.org/10.1136/bmj.b5349

Taguchi, M., Mishima, H., Shiozawa, Y., Hayashida, C., Kinoshita, A., Nannya, Y., Makishima, H., Horai, M., Matsuo, M., Sato, S., Itonaga, H., Kato, T., Taniguchi, H., Imanishi, D., Imaizumi, Y., Hata, T., Takenaka, M., Moriuchi, Y., Shiraishi, Y., … Miyazaki, Y. (2020). Genome analysis of myelodysplastic syndromes among atomic bomb survivors in Nagasaki. *Haematologica*, *105*(2), 358–365. Scopus. https://doi.org/10.3324/haematol.2019.219386

Takahashi, I., Abbott, R. D., Ohshita, T., Takahashi, T., Ozasa, K., Akahoshi, M., Fujiwara, S., Kodama, K., & Matsumoto, M. (2012). A prospective follow-up study of the association of radiation exposure with fatal and non-fatal stroke among atomic bomb survivors in Hiroshima and Nagasaki (1980-2003). *BMJ Open*, *2*(1). Scopus. https://doi.org/10.1136/bmjopen-2011-000654

Terayama, T., Shigemura, J., Kobayashi, Y., Kurosawa, M., Nagamine, M., Toda, H., & Yoshino, A. (2021). Mental health consequences for survivors of the 2011 Fukushima nuclear disaster: A systematic review. Part 2: Emotional and behavioral consequences. *CNS Spectrums*, *26*(1), 30–42. Scopus. https://doi.org/10.1017/S1092852920000115

Yamada, M., Furukawa, K., Tatsukawa, Y., Marumo, K., Funamoto, S., Sakata, R., Ozasa, K., Cullings, H. M., Preston, D. L., & Kurttio, P. (2021). Congenital Malformations and Perinatal Deaths Among the Children of Atomic Bomb Survivors: A Reappraisal. *American Journal of Epidemiology*, *190*(11), 2323–2333. Scopus. https://doi.org/10.1093/aje/kwab099

Yamada, M., Kasagi, F., Mimori, Y., Miyachi, T., Ohshita, T., & Sasaki, H. (2009). Incidence of dementia among atomic-bomb survivors—Radiation Effects Research Foundation Adult Health Study. *Journal of the Neurological Sciences*, *281*(1–2), 11–14. Scopus. https://doi.org/10.1016/j.jns.2009.03.003

Yamada, M., Sasaki, H., Kasagi, F., Akahoshi, M., Mimori, Y., Kodama, K., & Fujiwara, S. (2002). Study of cognitive function among the Adult Health Study (AHS) population in Hiroshima and Nagasaki. *Radiation Research*, *158*(2), 236–240. Scopus. https://doi.org/10.1667/0033-7587(2002)158[0236:SOCFAT]2.0.CO;2

Yousif, L., Blettner, M., Hammer, G. P., & Zeeb, H. (2010). Testicular cancer risk associated with occupational radiation exposure: A systematic literature review. *Journal of Radiological Protection*, *30*(3), 389–406. Scopus. https://doi.org/10.1088/0952-4746/30/3/R01

Appendix A: Critical appraisals for systematic reviews

Systematic reviews (with and without meta-analysis) were appraised for quality using the CASP Systematic Review checklist.[59]

Daniels, R. D., M. K. Schubauer-Berigan, R. D. Daniels, and M. K. Schubauer-Berigan. 'A Meta-Analysis of Leukaemia Risk from Protracted Exposure to Low-Dose Gamma Radiation'. *Occupational & Environmental Medicine* 68, no. 6 (2011): 457–64. https://doi.org/10.1136/oem.2009.054684.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	Do the [then] present risk estimates of leukaemia from low dose protracted ionising radiation reflect actual risks, given that present RREs are based on Japanese atomic bomb survivors?
2	Did the authors look for the right type of papers?	Yes	23 studies of leukaemia risk from protracted ionising radiation exposure.
3	Do you think all the important, relevant studies were included?	Yes	PubMed and EMBASE, in addition to summary information from the National Academies and United Nations.
4	Did the review's authors do enough to assess the quality of the included studies?	Yes	A thorough selection process is described.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	Yes	The process is thoroughly described.
Section B: What are the results?		**Comments**	

[59] Checklist available at https://casp-uk.net/images/checklist/documents/CASP-Systematic-Review-Checklist/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
6	What are the overall results of the review?	There is a significant association between leukaemia (excluding CLL) and protracted exposure to low-dose ionising radiation.	
7	How precise are the results?	Confidence intervals are provided.	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	Study populations were limited to occupational and environmental settings.
9	Were all important outcomes considered?	Yes	Limited to leukaemia excluding CLL.
10	Are the benefits worth the harms and costs?	Can't tell	

Hammer, G. P., U. Scheidemann-Wesp, F. Samkange-Zeeb, H. Wicke, K. Neriishi, and M. Blettner. 'Occupational Exposure to Low Doses of Ionizing Radiation and Cataract Development: A Systematic Literature Review and Perspectives on Future Studies'. *Radiation and Environmental Biophysics* 52, no. 3 (2013): 303–19. https://doi.org/10.1007/s00411-013-0477-6.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	Aims to identify epidemiological studies on cataracts and lens opacities induced by exposure to low-dose (that is, up to 1 Sv) ionising radiation.
2	Did the authors look for the right type of papers?	Yes	Searched PubMed and EMBASE, and the search strategy is thoroughly described.
3	Do you think all the important, relevant studies were included?	Yes	24 papers retained for review, including LSS, flight crew, astronauts, clean-up workers, nuclear workers, residents from contaminated areas, as well as medical workers.
4	Did the review's authors do enough to assess the quality of the included studies?	Can't tell	Studies were reviewed for their methodological quality, but there is no detail of how this review was conducted, or if any studies were subsequently excluded. Notably, most of the included studies were cross-sectional analyses, for which there is no validated quality assurance tool.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	Data was not pooled	
Section B: What are the results?		**Comments**	
6	What are the overall results of the review?	There is heterogeneity in the results with inconclusive evidence on the dose-response relationship.	
7	How precise are the results?	Confidence Intervals are included.	

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section C: Will the results help locally?		**Yes/Can’t Tell/No**	
8	Can the results be applied to the local population?	Yes	
9	Were all important outcomes considered?	Yes	
10	Are the benefits worth the harms and costs?	Can’t tell	

Hauptmann, M., R. D. Daniels, E. Cardis, H. M. Cullings, G. Kendall, D. Laurier, M. S. Linet, et al. 'Epidemiological Studies of Low-Dose Ionizing Radiation and Cancer: Summary Bias Assessment and Meta-Analysis'. *Journal of the National Cancer Institute - Monographs* 2020, no. 56 (2020): 188–200. https://doi.org/10.1093/JNCIMONOGRAPHS/LGAA010.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	Meta-analysis of articles published since 2006 that have reported excess cancer risks from low-dose exposures to ionising radiation, to assess the magnitude of the risk and whether positive findings could be explained by biases.
2	Did the authors look for the right type of papers?	Yes	Inclusions: Low-dose (≤100 mGy); risk estimates; published 2006 – 2017 (subsequent to *Biological effects of Ionizing Radiation VII* review, published in 2006.
3	Do you think all the important, relevant studies were included?	Yes	Clear and reasonable selection criteria resulted in 26 studies included. Exclusions are explained.
4	Did the review's authors do enough to assess the quality of the included studies?	Yes	This paper took a non-standard approach to quality, because it was interested in bias. The authors demonstrate that there is not always a direct relationship between quality and bias, with some high quality studies nonetheless being subject to bias; and others are deemed of low quality but do not have bias. They also question publication bias, noting that it can be difficult to publish an epidemiological study with a null or statistically non-significant finding.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	Yes	Adjustments were made where confidence intervals were 90% rather than 95%, which is an approximation and may skew the results. Separate meta-analysis were performed for solid cancers and leukaemia.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section B: What are the results?		**Comments**	
6	What are the overall results of the review?	The authors conclude that "there is now a large body of epidemiological data that supports excess cancer risks for low-dose ionizing radiation, and the magnitude of the excess relative cancer risk from these low dose studies is statistically compatible with the atomic bomb survivors" (p. 199).	
7	How precise are the results?	Confidence intervals are provided, illustrated by clear figures.	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	Appropriate populations were included.
9	Were all important outcomes considered?	Yes	Solid cancers and leukaemia.
10	Are the benefits worth the harms and costs?	Can't tell	

IARC Study Group on Cancer Risk among Nuclear Industry Workers. 'Direct Estimates of Cancer Mortality Due to Low Doses of Ionising Radiation: An International Study'. *Lancet* 344, no. 8929 (1994): 1039–43. https://doi.org/10.1016/S0140-6736(94)91706-X.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	The adequacy of [then] current protection standards, which were based on estimates from atomic bomb survivors and therapeutically irradiated patients.
2	Did the authors look for the right type of papers?	Yes	Papers were selected "on the basis of availability, dosimetric [which means 'measurement of radiation exposure'], demographic, follow-up and mortality data" (p. 1040).
3	Do you think all the important, relevant studies were included?	Can't tell	The included papers are relevant, but it is unclear if and why any were rejected.
4	Did the review's authors do enough to assess the quality of the included studies?	No	No discussion of this in the article.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	Yes	Similarities in the types of activities carried out at the seven facilities; outliers were excluded; dosimetry experts reviewed the practices across the facilities to ensure dose was reasonably measured; compensations are described for apparent biases.
Section B: What are the results?		**Comments**	
6	What are the overall results of the review?	The results supported the status quo in relation to [then] current radiation protection recommendations. That is, the results were sufficiently well aligned with those form the Japanese atomic bomb survivors' data.	
7	How precise are the results?	Confidence intervals are provided.	

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	It seems reasonable to assume that if the results for nuclear workers are substantially the same as for atomic bomb survivors, then they are likely to be similar for people exposed though their military occupations.
9	Were all important outcomes considered?	Yes	Solid cancer, and leukaemia excluding CLL.
10	Are the benefits worth the harms and costs?	Can't tell	

McGale, P., and S. C. Darby. 'Low Doses of Ionizing Radiation and Circulatory Diseases: A Systematic Review of the Published Epidemiological Evidence'. *Radiation Research* 163, no. 3 (2005): 247–57. https://doi.org/10.1667/RR3314.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	Review seeking other evidence in support of recent analyses that suggest atomic bomb survivors with an exposure in the range of 0-4 Sv experience high levels of circulatory system diseases.
2	Did the authors look for the right type of papers?	Yes	Searched for papers about stroke or heart disease patients who were exposed to 0-5 Gy or 0-5 Sv through sources other than atomic bomb.
3	Do you think all the important, relevant studies were included?	Yes	Study selection process is thorough, using MEDLINE, and well described.
4	Did the review's authors do enough to assess the quality of the included studies?	Can't tell	They describe a process of eliminating studies, but it was not based entirely on quality factors.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	Not a meta-analysis	
Section B: What are the results?		**Comments**	
6	What are the overall results of the review?	1/6 studies found evidence of an association between low-dose radiation exposure and circulatory diseases, and 5/6 studies did not find such an association.	
7	How precise are the results?	Confidence intervals are provided.	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	Includes a range of populations.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
9	Were all important outcomes considered?	Yes	This is a thorough review.
10	Are the benefits worth the harms and costs?	Can’t tell	

Ruhm, W., D. Laurier, and R. Wakeford. 'Cancer Risk Following Low Doses of Ionising Radiation - Current Epidemiological Evidence and Implications for Radiological Protection'. *Mutation Research - Genetic Toxicology and Environmental Mutagenesis* 873 (2022): 503436. https://doi.org/10.1016/j.mrgentox.2021.503436.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	Radiation-related cancer risks from low-LET radiation in the order of 100 mGy. Focus is on acute, repeated or chronic exposures. Note: Authors do not describe the paper as a systematic review, but "a discussion of scientific reviews published about radiation-related cancer risks" (p. 2) subsequent to reviews by the US National Academy of Sciences in 2006, and the United Nations Scientific Committee on the Effects of Radiation in 2008.
2	Did the authors look for the right type of papers?	Yes	Specifically includes studies of Japanese atomic bomb survivors, from the highly regarded RERF LSS cohort; and solid cancer amongst nuclear workers is also discussed.
3	Do you think all the important, relevant studies were included?	Yes	As above.
4	Did the review's authors do enough to assess the quality of the included studies?	No	The quality of RERF Life Span Studies (LSS cohort) seems to be assumed. In other sections of the paper, the quality of the studies is described.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	N/A	This is not a meta-analysis.
Section B: What are the results?		**Comments**	

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
6	What are the overall results of the review?	From the abstract: "In summary, substantial evidence was found from epidemiological studies of exposed groups of humans that ionizing radiation causes cancer at acute and protracted doses above 100 mGy, and growing evidence for doses below 100 mGy. The significant radiation-related solid cancer risks observed at doses of several 100 mGy of protracted exposures (observed, for example, among nuclear workers) demonstrate that doses accumulated over many years at low dose rates do cause stochastic [random probability distribution] health effects" (p. 1).	
7	How precise are the results?	Confidence intervals from included studies are provided where available. Conclusion states: "As follow-up of populations continues, and as efforts are made to pool the data from some of these studies – both of which should increase statistical power – we would expect improved detection of radiation-related excess rates in cancer and leukaemia below 100 mGy in future, at least as long as all cancers are analysed together" (p. 15).	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	The review specifically includes populations of interest to this present review.
9	Were all important outcomes considered?	Yes	A considerable array of populations and cancer incidence outcomes are included, including meta-analyses studies.
10	Are the benefits worth the harms and costs?	Yes	The review brings together a wide range of recent research findings.

Terayama, T., J. Shigemura, Y. Kobayashi, M. Kurosawa, M. Nagamine, H. Toda, and A. Yoshino. ‘Mental Health Consequences for Survivors of the 2011 Fukushima Nuclear Disaster: A Systematic Review. Part 2: Emotional and Behavioral Consequences’. *CNS Spectrums* 26, no. 1 (2021): 30–42. https://doi.org/10.1017/S1092852920000115.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can’t Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	From the abstract: “To compile the findings of studies assessing emotional and behavioral changes in the survivors of the 2011 Fukushima nuclear disaster” (p. 30).
2	Did the authors look for the right type of papers?	Yes	Search strategy is detailed and thorough. Fukushima prefecture residents either before or after the Fukushima nuclear disaster and who experienced any disaster-related exposure. Emotional consequences (e.g., perceptions of the nuclear disaster) and behavioural consequences (e.g., suicidal attempts).
3	Do you think all the important, relevant studies were included?	Can’t tell	English or Japanese. PubMed, PsycINFO, Psychology and Behavioral Sciences Collection, and ICHUSHI databases. It is unclear if there was follow up from reference lists or experts contacted. No unpublished studies were included.
4	Did the review’s authors do enough to assess the quality of the included studies?	Can’t tell	PRISMA statement included. Included observational studies but not conference proceedings or meeting abstracts. Studies with a sample size of <10 were excluded from the review.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
			The authors outlined the number of types of study (e.g., longitudinal) and data (e.g., self-report) included. It is unclear whether any other quality assessments or appraisals were made.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	N/A	Not a meta-analysis.
Section B: What are the results?		**Comments**	
6	What are the overall results of the review?	From the abstract: "The Fukushima nuclear disaster survivors suffered issues in risk perception, well-being, stigmatization, and alcohol/tobacco use in the first 8 years after the disaster" (p. 30). As well as increased completed suicide attempts.	
7	How precise are the results?	p-values or confidence intervals not reported.	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	The review specifically includes populations of interest to this present review.
9	Were all important outcomes considered?	Yes	A wide range of important outcomes were examined.
10	Are the benefits worth the harms and costs?	Can't tell	

Yousif, L., M. Blettner, G. P. Hammer, and H. Zeeb. 'Testicular Cancer Risk Associated with Occupational Radiation Exposure: A Systematic Literature Review'. *Journal of Radiological Protection* 30, no. 3 (2010): 389–406. https://doi.org/10.1088/0952-4746/30/3/R01.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section A: Are the results of the review valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the review address a clearly focused issue?	Yes	The relationship between occupational radiation exposure (ionising and non-ionising) and testicular cancer. Of interest to this review, the study included 31 articles concerning ionising radiation.
2	Did the authors look for the right type of papers?	Yes	Case control (n=7) and cohort (n=30) studies included, with a range of occupational groups including radiation workers, military, aircrew, and medical exposure. Papers from 1990 to 2008.
3	Do you think all the important, relevant studies were included?	Yes	Searched MEDLINE, PubMed, EMBASE, and SCISEARCH, (plus grey literature sources, which yielded zero returns). Thorough search strategy is described, and a study protocol documented prior to search commencing. This literature review includes a New Zealand study: Pearce et al. (1990) *Follow up of New Zealand participants in British atmospheric nuclear weapons test in the Pacific*, published in the British Medical Journal.
4	Did the review's authors do enough to assess the quality of the included studies?	Yes	Bias was checked using a modified version of the Effective Public Health Practice Project checklist, with two relevant criteria added. Risk bias ratings are provided. PRISMA statement included.
5	If the results of the review have been combined [meta-analysis], was it reasonable to do so?	N/A	Authors state that pooled analysis was not conducted due to heterogeneity.

CASP Checklist for Systematic Reviews (with and without meta-analysis)			
Section B: What are the results?		**Comments**	
6	What are the overall results of the review?	"There was very little evidence for associations between occupational ionizing radiation and testicular cancer" (p. 389).	
7	How precise are the results?	Confidence intervals are provided.	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
8	Can the results be applied to the local population?	Yes	
9	Were all important outcomes considered?	Yes	Strong focus on addressing the research question.
10	Are the benefits worth the harms and costs?	Can't tell	

Appendix B: Critical appraisals for cohort studies

Cohort studies were appraised for quality using the CASP Cohort Study checklist.[60]

Adams, M. J., E. J. Grant, K. Kodama, Y. Shimizu, F. Kasagi, A. Suyama, R. Sakata, and M. Akahoshi. 'Radiation Dose Associated with Renal Failure Mortality: A Potential Pathway to Partially Explain Increased Cardiovascular Disease Mortality Observed after Whole-Body Irradiation'. *Radiation Research* 177, no. 2 (2012): 220–28. https://doi.org/10.1667/RR2746.1.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Exploring LSS data for an association between increased hypertension, chronic renal failure: is the risk of cardiovascular disease (CVD) in full-body exposed persons mediated at least in part through chronic renal dysfunction?
2	Was the cohort recruited in an acceptable way?	Yes	LSS standards; exposed within 10km of hypocentres, invited to participate in mail survey.
3	Was the exposure accurately measured to minimise bias?	Yes	LSS.
4	Was the outcome accurately measured to minimise bias?	Yes	
5a	Have the authors identified all confounding factors?	Yes	Especially diabetes.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	
6a	Was the follow-up of subjects complete enough?	Yes	LSS.
6b	Was the follow up of subjects long enough?	Yes	LSS.

[60] Checklist available at https://casp-uk.net/images/checklist/documents/CASP-Cohort-Study-Checklist/CASP-Cohort-Study-Checklist-2018_fillable_form.pdf

CASP Checklist for cohort studies			
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	That renal dysfunction could be part of the mechanism causing increased CVD risk after whole-body irradiation.	
8	How precise are the results?	Some data is from self-reports: information on hypertension and diabetes.	
9	Do you believe the results?	Yes	Noting that the authors comment that further research is required; and that the effect was only evident using the broadest definition of Chronic Renal Failure.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Most effect seems to be in people aged <40 at exposure.
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?		Recognising the possible link between renal failure and CVD.

Bazyka, D., Ilienko, I., Golyarnik, N., Belyaev, O., and Lyaskivska,O. 'Gene Expression and Cellular Markers of Occupational Radiation Exposure in Chernobyl Shelter Construction Workers'. *Health Physics,* Vol.199 (2020):37-43) https://doi.org/10.1097/HP.0000000000001277.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The study focused on the influence of borderline exposure to annual professional limits and age on expression of molecular markers.
2	Was the cohort recruited in an acceptable way?	Yes	Cohort recruited from staff performing shift professional activities at the shelter inside the contaminated area of the 30-km Chernobyl exclusion zone. Health check before exposure including immunological analysis and exclusion of staff close to the annual limit of 20 mSv. Inclusion criteria: absence of cancer, chronic non-cancer and infectious diseases, blood and immunity disorders, and past radiation exposure working at Chernobyl or in exclusion zone.
3	Was the exposure accurately measured to minimise bias?	Yes	"Dosimetry included daily external dose registration with thermoluminescence dosimeters and internal dose assessment by radiochemistry of feces and urine" (p. 38).
4	Was the outcome accurately measured to minimise bias?	Yes	Standard biomolecular techniques were used to create comparable results.
5a	Have the authors identified all confounding factors?	Can't tell	Only outline controlling for age and dosage.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	For age and dosage these are considered in both the design and the analysis.
6a	Was the follow-up of subjects complete enough?	Yes	Blood samples were taken on the first day of the subject's visit to hospital 7-14 days after exit from the radiation zone. No mention if any participants were lost to follow-up.

CASP Checklist for cohort studies			
6b	Was the follow up of subjects long enough?	Can't tell	It was long enough for there to be significant changes in gene expression.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	This study demonstrates DNA damage following radiation exposure and a higher susceptibility to exposure is demonstrated in workers aged younger than 40 years old. "Obtained data testify to a non-linear type of response of gene regulators of cell survival and apoptosis after exposure to radiation doses below 50 mSv" (p. 42).	
8	How precise are the results?	Confidence intervals are provided for all measured gene expression and those genes with significant differences identified.	
9	Do you believe the results?	Yes	The results are adequately presented and how the results support the conclusions is clear.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Authors note similar studies that have identified changes in molecular markers following exposure to radiation.
12	What are the implications of this study for practice?		The study suggests greater DNA damage may occur for those under 40 years old when exposed to radiation near safe working limits and identifies molecular markers that could indicate mechanisms for later epidemiological effects of radiation exposure.

Bockwoldt, B., H. Sugiyama, K. Tsai, P. Bhatti, A. V. Brenner, A. Hu, K. F. Kerr, E. Morenz, B. French, and A. I. Phipps. 'Gastrointestinal Cancer Survival and Radiation Exposure among Atomic Bomb Survivors: The Life Span Study'. *Cancer Epidemiology Biomarkers and Prevention* 30, no. 2 (2021): 412–18. https://doi.org/10.1158/1055-9965.EPI-20-1239.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Does prior exposure to ionising radiation (LSS cohort) result in increased mortality risk amongst people who are later diagnosed with gastrointestinal cancers?
2	Was the cohort recruited in an acceptable way?	Yes	Subset from the LSS: n=7,728.
3	Was the exposure accurately measured to minimise bias?	Yes	Exposure is well defined for LSS; and the study adjusted for city of primary exposure.
4	Was the outcome accurately measured to minimise bias?	Yes	Mortality.
5a	Have the authors identified all confounding factors?	Can't tell	
5b	Have they taken account of the confounding factors in the design and/or analysis?	Can't tell	
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	Diagnosis between 1958 – 2009; with follow-up from 1958 - 2014.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	No statistically significant association was observed between dose and survival among LSS participants with gastrointestinal cancer. The results are inconclusive.	
8	How precise are the results?	95% CI: 0.9, 2.12.	

CASP Checklist for cohort studies			
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?	Can't tell	

Boice, J. D., S. S. Cohen, M. T. Mumma, D. A. Hagemeyer, H. Chen, A. P. Golden, R. C. Yoder, and L. T. Dauer. 'Mortality from Leukemia, Cancer and Heart Disease among U.S. Nuclear Power Plant Workers, 1957-2011'. *International Journal of Radiation Biology* 98, no. 4 (2022): 657–78. https://doi.org/10.1080/09553002.2021.1967507.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Use SMR analysis to examine the level of radiation risk when exposure is chronic (gradual, over time), rather than acute, as in the case of atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	A subset of the MPS. 15 percent of the MPS are nuclear power plant workers (n=135,193, of which 29,076 had died before 2012, having been followed up for an average of 30.2 years). The study was restricted to those first employed prior to 1985 (based on likely exposures) who were employed for at least 30 days.
3	Was the exposure accurately measured to minimise bias?	Yes	"Radiation doses from all places of employment were sought by linking the study roster to the Radiation Exposure Monitoring System (REMS) maintained by the U.S. Department of Energy" (p. 661).
4	Was the outcome accurately measured to minimise bias?	Yes	The authors described the methods used to minimise bias.
5a	Have the authors identified all confounding factors?	Yes	Where there was no smoking data, socioeconomic status was used as a proxy measure, but the possibilities of confounding are recognised as a limitation.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Used Cox proportional hazards models, adjusting for sex, year of birth, and socioeconomic status.
6a	Was the follow-up of subjects complete enough?	Yes	Data from 1957 to 1984 was included, with follow-up from 1969. Follow-up continued for each person until their death,

CASP Checklist for cohort studies			
			until they turned 95 years of age, or until 31 December 2011 – whichever came first.
6b	Was the follow up of subjects long enough?	Yes	Most subjects were followed for 30 years or more, and most were employed as nuclear workers for 20 years or more.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Prolonged exposure to radiation increased the risk of leukaemia (excluding CLL) among nuclear power plant workers; but there was little evidence of an association for radiation exposure and all solid cancers.	
8	How precise are the results?	Confidence intervals are provided.	
9	Do you believe the results?	Yes	Study is well presented and seems very thorough.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Although the long exposure (20 years or more) seems likely to be longer than what would be experienced by NZ veterans.
11	Do the results of this study fit with other available evidence?	Yes	Authors note contrast with results based on LSS, attributing the variance to different risks through acute and chronic exposures.
12	What are the implications of this study for practice?	Can't tell	

Boice, J. D., Jr., S. S. Cohen, M. T. Mumma, A. P. Golden, S. C. Howard, D. J. Girardi, E. D. Ellis, et al. 'Mortality among Workers at the Los Alamos National Laboratory, 1943-2017'. *Int J Radiat Biol* 98, no. 4 (2022): 722–49. https://doi.org/10.1080/09553002.2021.1917784.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Compares SMR for study population with general population (based on white males and females).
2	Was the cohort recruited in an acceptable way?	Yes	MPS study.
3	Was the exposure accurately measured to minimise bias?	Yes	Exposure to radiation.
4	Was the outcome accurately measured to minimise bias?	Yes	Less than 0.1 percent lost to study; extensive efforts to obtain death certificates for 15,737 workers; cause of death established for all but 1.4 percent (n=220).
5a	Have the authors identified all confounding factors?	Yes	Adjusted for socioeconomic status, smoking, and education.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	Some of the data goes back 75 years, to the first test.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	The study failed to reveal significant associations between radiation dose and cancers of the lung, liver, and NHL, nor excesses in leukaemia or IHD.	
8	How precise are the results?	Confidence intervals are included.	
9	Do you believe the results?	Yes	Very thoroughly reported.

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?	Can't tell	

Cullings, H. M. 'Impact on the Japanese Atomic Bomb Survivors of Radiation Received from the Bombs'. *Health Physics* 106, no. 2 (2014): 281–93. https://doi.org/10.1097/HP.0000000000000009.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Radiation impacts on a variety of health impacts from the bombs at Hiroshima and Nagasaki.
2	Was the cohort recruited in an acceptable way?	Yes	RERF/LSS cohort.
3	Was the exposure accurately measured to 97inimize bias?	Yes	Measured distance from blasts and doses in colon.
4	Was the outcome accurately measured to minimise bias?	Yes	LSS follow-up.
5a	Have the authors identified all confounding factors?	Can't tell	Some mention of confounding factors but no distinct analysis as it is a review.
5b	Have they taken account of the confounding factors in the design and/or analysis?	N/A	
6a	Was the follow-up of subjects complete enough?	Yes	LSS is the most complete follow-up data set.
6b	Was the follow up of subjects long enough?	Yes	LSS is the most complete follow up-data set.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Review summarises the total impact of the bombs dropped at Hiroshima and Nagasaki.	
8	How precise are the results?	The RERF data set is reported to be the most complete collection of information in the world on the health effects experienced by the survivors of the atomic bombs dropped at Hiroshima and Nagasaki.	
9	Do you believe the results?	Can't tell	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Although specific to survivors of Hiroshima and Nagasaki atomic bombs.
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?		Mixed evidence on exposure dose measure and health effects among the RERF population.

Fujihara, M., R. Sakata, N. Yoshida, K. Ozasa, D. L. Preston, and K. Mabuchi. 'Incidence of Lymphoid Neoplasms among Atomic Bomb Survivors by Histological Subtype, 1950 to 1994'. *Blood* 139, no. 2 (2022): 217–27. https://doi.org/10.1182/blood.2020010475.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Examine radiation exposure effects from diagnoses between 1950 and 1994 (these being prior to the WHO classification of tumors of hematopoietic and lymphoid tissues).
2	Was the cohort recruited in an acceptable way?	Yes	Used data from established registries and RERF databases including LSS.
3	Was the exposure accurately measured to minimise bias?	Can't tell	Describes a history of past reclassifications that would likely introduce a degree of bias.
4	Was the outcome accurately measured to minimise bias?	Yes	Their selection process included a pathology panel review.
5a	Have the authors identified all confounding factors?	Yes	Adjusted for city of exposure, and period of exposure.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Adjustments are described.
6a	Was the follow-up of subjects complete enough?	Yes	LSS protocols.
6b	Was the follow up of subjects long enough?	Yes	LSS.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	A significant dose-response for NHL neoplasms amongst males (but not females); with subtype analyses showing radiation dose was strongly associated with increased precursor cell neoplasms rates, with an estimated ERR per Gy of 16 (95% CI: 7.0, >533) at age 50.	
8	How precise are the results?	95% confidence intervals are provided.	

CASP Checklist for cohort studies			
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?		Strengthens knowledge base.

Fujimura, K., A. Sugiyama, T. Akita, M. Ohisa, S. Nagashima, K. Katayama, R. Maeda, and J. Tanaka. 'Screening for M-Proteinemia Consisting of Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma for 30 Years among Atomic Bomb Survivors in Hiroshima'. *International Journal of Hematology* 113, no. 4 (2021): 576–85. https://doi.org/10.1007/s12185-020-03045-y.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The study looked at the prevalence and incidence of M-proteinemia[61] in atomic bomb survivors during a 30-year period (198-2018) to examine the influence of atomic bomb radiation exposure on the occurrence of M-proteinemia and whether it is a late radiation effect among atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	The cohort was selected from 39,164 atomic bomb survivors who had received comprehensive health examinations and consented to the M-protein screening test between September 1989 and September 1990. Individuals with missing data about exposure or exposure to black rain away from the hypocentre were excluded, leaving 38,602 survivors who were analysed for M-proteinemia from 1989 to 2018.
3	Was the exposure accurately measured to minimise bias?	Yes	Exposure to radiation was based on the four categories used by the administrative office in Hiroshima city: direct exposure group, entrant group, relief group, and prenatal group.
4	Was the outcome accurately measured to minimise bias?	N/A	Individuals were screened for MGUS and M-proteinemia with biomolecular techniques.

[61] M-proteinemia includes a wide range of disease states, from monoclonal gammopathy of undetermined significance (MGUS), which is a premalignant state, to malignant states such as multiple myeloma, macroglobulinemia, malignant lymphoma, and amyloidosis.

CASP Checklist for cohort studies			
5a	Have the authors identified all confounding factors?	Yes	Gender, age at exposure, and exposure category were controlled for. The authors also note the impact of ethnicity, which is not corrected for. This may affect the generalisability of the results as other studies have identified M-proteinemia occurs less commonly in Asian populations when compared to American populations.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	A regression analysis is used to control for gender, age at exposure, and exposure category. The authors acknowledge that the study is limited, as no data was available for patients who died before 1985.
6a	Was the follow-up of subjects complete enough?	Yes	The individuals were part of an annual comprehensive health examination offered free to atomic bomb survivors twice a year since 1968. Screening for M-proteinemia was started in 1988.
6b	Was the follow up of subjects long enough?	Yes	See comment to 6a.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	The authors found that “the prevalence of M-proteinemia was 2.4% and the incidence of MGUS was 1.8% for 30 years in the A-bomb survivor cohort in Hiroshima. They were not statistically significant association with radiation exposure category. However, the risk of prevalence of M-proteinemia at 70 years and incidence of MGUS were significantly higher in males and in persons aged < 20 years at the time of exposure, indicating that exposure to environmental factors at a young age may be important to developing MGUS with age” (p. 584).	
8	How precise are the results?	P ratios and 95% confidence intervals calculated.	
9	Do you believe the results?	Yes	Although a limited cohort.

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Although specific to people that were exposed to an atomic bomb and are over 70 years old.
11	Do the results of this study fit with other available evidence?	No	There is currently no consensus about the influence of radiation exposure to the development of MGUS particularly for Hiroshima atomic bomb survivors.
12	What are the implications of this study for practice?		Individuals exposed to an atomic bomb who are male or under the age of 20 years old at the time of exposure should be followed up regularly as they may be at increased risk of M-proteinemia or MGUS later in life.

Fujiwara, S., A. Suyama, J. B. Cologne, M. Akahoshi, M. Yamada, G. Suzuki, K. Koyama, et al. 'Prevalence of Adult-Onset Multifactorial Disease among Offspring of Atomic Bomb Survivors'. *Radiation Research* 170, no. 4 (2008): 451–57. https://doi.org/10.1667/RR1392.1.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Parental exposure and the risk of adult multifactorial diseases.
2	Was the cohort recruited in an acceptable way?	Yes	Used a mail survey and attained a 50 percent response rate.
3	Was the exposure accurately measured to minimise bias?	Yes	F1 mortality follow-up cohort and dose estimates.
4	Was the outcome accurately measured to minimise bias?	Yes	Used a series of health examinations administered by clinicians.
5a	Have the authors identified all confounding factors?	Yes	Identified common risk factors for these diseases.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Appropriate analysis used and adjusted results presented.
6a	Was the follow-up of subjects complete enough?	Yes	Looked at adult-onset diseases in adulthood.
6b	Was the follow up of subjects long enough?	Yes	Looked at adult-onset diseases in adulthood.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	No association of the health outcomes of interest.	
8	How precise are the results?	Based on medical examination.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Have discussed other evidence in their discussion.
12	What are the implications of this study for practice?		Future prospective research is needed, follow-up through later stages of life may present more evidence.

Grant, E. J., K. Furukawa, R. Sakata, H. Sugiyama, A. Sadakane, I. Takahashi, M. Utada, Y. Shimizu, and K. Ozasa. 'Risk of Death among Children of Atomic Bomb Survivors after 62 Years of Follow-up: A Cohort Study'. *Lancet Oncology* 16, no. 13 (2015): 1316–23. https://doi.org/10.1016/S1470-2045(15)00209-0.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Radiation risks of death caused by cancer or non-cancer diseases among children of survivors of atomic bombs.
2	Was the cohort recruited in an acceptable way?	Yes	Recruited from national census and were interviewed.
3	Was the exposure accurately measured to minimise bias?	Yes	Exposure based on distance.
4	Was the outcome accurately measured to minimise bias?	Yes	Cause of death data and used WHO international classifications of diseases.
5a	Have the authors identified all confounding factors?	Yes	Have adjusted for some confounding factors in their analysis.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Have adjusted for some confounding factors in their analysis.
6a	Was the follow-up of subjects complete enough?	Yes	Followed up participants until death.
6b	Was the follow up of subjects long enough?	Yes	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	No associations between parental radiation exposure and mortality among children.	
8	How precise are the results?	I would say precise.	
9	Do you believe the results?	Yes	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	They have identified and discussed other studies with similar results.
12	What are the implications of this study for practice?		There is more research needed and continued follow-up.

Grant, E. J., M. Yamamura, A. V. Brenner, D. L. Preston, M. Utada, H. Sugiyama, R. Sakata, K. Mabuchi, and K. Ozasa. 'Radiation Risks for the Incidence of Kidney, Bladder and Other Urinary Tract Cancers: 1958-2009'. *Radiation Research* 195, no. 2 (2021): 140–48. https://doi.org/10.1667/RADE-20-00158.1.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Risks of UTC (n=790) and kidney cancer (n=218) among atomic bomb survivors (LSS).
2	Was the cohort recruited in an acceptable way?	Yes	LSS.
3	Was the exposure accurately measured to minimise bias?	Yes	LSS.
4	Was the outcome accurately measured to minimise bias?	Yes	Methods thoroughly described.
5a	Have the authors identified all confounding factors?	Yes	Focus on smoking.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Adjusted for smoking.
6a	Was the follow-up of subjects complete enough?	Yes	LSS.
6b	Was the follow up of subjects long enough?	Yes	52-year follow-up.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Strong linear radiation dose-response for UTC; no association for kidney cancer.	
8	How precise are the results?	Confidence intervals are included.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Yes	Relevant acute exposure.
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?	Can't tell	

Hayashi, T., K. Furukawa, Y. Morishita, I. Hayashi, N. Kato, K. Yoshida, Y. Kusunoki, S. Kyoizumi, and W. Ohishi. 'Intracellular Reactive Oxygen Species Level in Blood Cells of Atomic Bomb Survivors Is Increased Due to Aging and Radiation Exposure'. *Free Radical Biology and Medicine* 171 (2021): 126–34. https://doi.org/10.1016/j.freeradbiomed.2021.05.017.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The study investigated the relationship between intracellular levels of reactive oxygen species in blood cells or T cell subsets and serum iron, ferritin, and C-reactive protein levels, as well as how these variables are affected by age and radiation exposure in atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	They selected 2,495 subjects from the AHS participants of Hiroshima and who visited the RERF for clinical health examination from 2007 to 2012. As they were studying biomarkers associated with inflammations they confirmed the absence of additional radiation exposure, such as radiotherapy, and excluded participants who had cancer or inflammation-associated diseases (e.g., current cold, chronic bronchitis, collagen disease, and arthritis).
3	Was the exposure accurately measured to minimise bias?	Yes	The radiation exposure dose for each individual was estimated using bone marrow doses calculated using the dosimetry system DS02.
4	Was the outcome accurately measured to minimise bias?	Yes	Standard biomedical techniques were used to do cell analysis and a newly developed assay to measure reactive oxygen species in blood immune cells.
5a	Have the authors identified all confounding factors?	No	They controlled for sex, age at examination, smoking status, alcohol consumption, body mass index, time of blood

CASP Checklist for cohort studies			
			sampling, and serum iron, ferritin, and C-reactive protein levels.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	A multivariate linear regression analysis was used for body mass index, smoking status, alcohol consumption, and blood collection times. Sex, age, and radiation dose were correlated with reactive oxygen species levels.
6a	Was the follow-up of subjects complete enough?	Yes	Blood samples from 2007 to 2012 were used.
6b	Was the follow up of subjects long enough?	Yes	All participants were enrolled from a long-term cohort study, the AHS.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	The reactive oxygen species levels in blood immune cells are elevated due to radiation exposure 60 years prior, especially in monocytes, granulocytes, and cytotoxic effector T cells, potentially participating in tissue-damaging responses in the body and contribute to inflammation.	
8	How precise are the results?	A p-value of less than 0.05 was used to test for significance.	
9	Do you believe the results?	Yes	The new assay appears to be able to detect reactive oxygen species in blood cells and elevated levels of reactive oxygen species in the blood cells of those who have had a high-dose radiation exposure 60 years after the exposure.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	The results would only apply to those exposed to high-dose radiation.

CASP Checklist for cohort studies			
11	Do the results of this study fit with other available evidence?	Yes	It is known that high-dose radiation causes changes in the functioning of the immune system – this study is looking for a possible mechanism for these changes.
12	What are the implications of this study for practice?		Anyone exposed to high-dose radiation may have decreased immune function, increased inflammatory states and increased reactive oxygen species in their blood cells, although the link to disease has not been established.

Iwanaga, M., Hsu, W., Soda, M., Takasaki, Y., Tawara, M., Joh, T., Amenomori, T., Yamamura, M., Yoshida, Y., Koba, T., Miyazaki, Y., Matsuo, T., Preston, DL., Suyama, A., Kodama, K., and Tomonaga, M. 'Risk of Myelodysplastic Syndromes in People Exposed to Ionizing Radiation: A Retrospective Cohort Study of Nagasaki Atomic Bomb Survivors' *Journal of Clinical Oncology* 29, no. 4 (2011) 428-434. DOI: 10.1200/JCO.2010.31.3080

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The aim of the study was to assess MDS risk and the radiation dose-response relationship 40 to 60 years after exposure through a retrospective review of clinical records.
2	Was the cohort recruited in an acceptable way?	Yes	Patients with MDS were identified across the two databases from five hospitals from 1982-2004. Clinical information was reviewed by haematologists and classified for MDS for into definite, possible, undetermined or non-MDS. Misdiagnosed and those outside the catchment area were excluded, leaving 605 eligible patients with MDS. A group of those exposed to radiation who developed MDS was also identified from ADBI and the LSS. To identify MDS in those exposed to radiation the MDS patient group was data linked to the those exposed to radiation in the ABDI and LSS databases.
3	Was the exposure accurately measured to minimise bias?	Can't tell	Exposure status was as recorded in the ABDI and LSS databases. Risk analyses were performed only with known exposure distances or dose.
4	Was the outcome accurately measured to minimise bias?	Yes	Review of the clinical information was conducted by skilled haematologists with standardised rating tools.
5a	Have the authors identified all confounding factors?	Yes	Those with MDS who were exposed to chemotherapy or radiation treatment were excluded. Sex, age at exposure,

CASP Checklist for cohort studies			
			and attained age/time since exposure were factors controlled for.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Cox regression models were used to assess the effects of sex, age at exposure, exposure distance, and dose on MDS incidence rates.
6a	Was the follow-up of subjects complete enough?	Yes	Participants were sourced from within long term cohort studies for those exposed to radiation or from existing clinical records where patients were receiving treatment.
6b	Was the follow up of subjects long enough?	Yes	Participants were sourced from within long term cohort studies for those exposed to radiation or from existing clinical records where patients were receiving treatment.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	They found a significant linear relationship between radiation dose and MDS risk among atomic bomb survivors. MDS rates were higher for men than for women and increased with age at exposure. MDS rates also increased with decreasing distance from the hypocentre and with increasing estimated dose. MDS followed a different pattern to radiation-induced leukaemia with MDS risk still existing 40 or more years after exposure and radiation-induced leukaemia peaking 10-15 years after exposure.	
8	How precise are the results?	p-values and confidence intervals included.	
9	Do you believe the results?	Yes	Although the numbers are small the association is significant.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Can’t tell	The study findings apply to those exposed to radiation from an atomic bomb within 3km of the hypocentre.
11	Do the results of this study fit with other available evidence?	Yes	Exposure to radiation is known to cause genetic damage which can lead to disease later in life.
12	What are the implications of this study for practice?		Long term follow-up of people who have been exposed to radiation should be conducted “to detect MDS as early as possible and reduce the risk of leukemic transformation by using new drugs such as DNA hypomethylating agents” (p. 434).

Kiuru, A., A. Auvinen, M. Luokkamaki, K. Makkonen, T. Veidebaum, M. Tekkel, M. Rahu, et al. 'Hereditary Minisatellite Mutations among the Offspring of Estonian Chernobyl Cleanup Workers'. *Radiation Research* 159, no. 5 (2003): 651–55. https://doi.org/10.1667/0033-7587%282003%29159%5B0651:HMMATO%5D2.0.CO;2.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Parental exposure at Chernobyl and genetic mutations in children.
2	Was the cohort recruited in an acceptable way?	Yes	Recruited from families who had a father involved in the clean-up.
3	Was the exposure accurately measured to minimise bias?	Yes	Exposure was involvement in the clean-up.
4	Was the outcome accurately measured to minimise bias?	Yes	Blood sampling and DNA extraction.
5a	Have the authors identified all confounding factors?	Yes	Examined multiple statistical analysis.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	As above.
6a	Was the follow-up of subjects complete enough?	N/A	
6b	Was the follow up of subjects long enough?	N/A	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	The study found that children born after the Chernobyl disaster had a slightly higher number of mutations, but these findings were not statistically significant.	
8	How precise are the results?	Precise, used complex genetic methods.	
9	Do you believe the results?	Yes	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	But limited by differences in radiation exposures.
12	What are the implications of this study for practice?	Can't tell	They haven't stated any.

Leuraud, K., D. B. Richardson, E. Cardis, R. D. Daniels, M. Gillies, J. A. O'Hagan, G. B. Hamra, et al. 'Ionising Radiation and Risk of Death from Leukaemia and Lymphoma in Radiation-Monitored Workers (INWORKS): An International Cohort Study'. *Lancet Haematology* 2, no. 7 (2015): e276–81. https://doi.org/10.1016/S2352-3026(15)00094-0.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Determining excess incidence of leukaemia among radiation-monitored workers.
2	Was the cohort recruited in an acceptable way?	Yes	Ethical adherence processes are described.
3	Was the exposure accurately measured to minimise bias?	Yes	Regulated radiation monitoring.
4	Was the outcome accurately measured to minimise bias?	Yes	
5a	Have the authors identified all confounding factors?	Yes	Smoking, socioeconomic status, exposure to benzene.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Sensitivity analyses conducted regarding benzene exposure.
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	Mean follow-up of 27 years.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Strong evidence of an association between protracted low-dose radiation exposure and leukaemia mortality.	
8	How precise are the results?	90% confidence intervals are included.	
9	Do you believe the results?	Yes	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Well-aligned with results from studies with acutely exposed populations.
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?		Importance of protection from radiation exposure.

Li, C. I., N. Nishi, J. A. McDougall, E. O. Semmens, H. Sugiyama, M. Soda, R. Sakata, et al. 'Relationship between Radiation Exposure and Risk of Second Primary Cancers among Atomic Bomb Survivors'. *Cancer Research* 70, no. 18 (2010): 7187–98. https://doi.org/10.1158/0008-5472.CAN-10-0276.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The relationship between first and second primary cancers in atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	LSS.
3	Was the exposure accurately measured to minimise bias?	Yes	LSS.
4	Was the outcome accurately measured to minimise bias?	Yes	LSS.
5a	Have the authors identified all confounding factors?	No	They note that they lacked information on risks such as cigarette smoking, alcohol use, and family history.
5b	Have they taken account of the confounding factors in the design and/or analysis?	No	
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	To 2022.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Survivors of solid cancers need to be carefully screened for subsequent primary cancers.	
8	How precise are the results?	Extensive tables provided, including confidence intervals.	
9	Do you believe the results?	Yes	Plausible explanations.

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Can't tell	No other research on second primary cancers encountered.
12	What are the implications of this study for practice?		Need for ongoing screening.

Loganovsky, K., J. M. Havenaar, N. L. Tintle, L. T. Guey, R. Kotov, and E. J. Bromet. 'The Mental Health of Clean-up Workers 18 Years after the Chernobyl Accident'. *Psychological Medicine* 38, no. 4 (2008): 481–88. https://doi.org/10.1017/S0033291707002371.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	"This study describes the long-term psychological effects of Chernobyl in a sample of clean-up workers in Ukraine" (p. 481). To assess depressive disorders, anxiety disorders, post-traumatic stress disorder, alcohol abuse, IED, suicide ideation, severe or frequent headaches, and days lost from work.
2	Was the cohort recruited in an acceptable way?	Yes	The sample of clean-up workers was selected from the State Registry of Ukraine. The cohorts were 295 male clean-up workers sent to Chernobyl between 1986 and 1990. Not being treated for acute radiation syndrome.
3	Was the exposure accurately measured to minimise bias?	Yes	"A three-level exposure variable was created. High exposure was defined as working on the roof or in the industrial site between April and October 1986 when radiation exposure was greatest (n=45). The remaining clean-up workers in the 1986–87 cohort worked in less contaminated areas and were classified as having moderate exposure (n=100). The 1988–90 group (n=150) had lower radiation exposure (Hatch et al. 2005; The Chernobyl Forum, 2006)" (p. 483).
4	Was the outcome accurately measured to minimise bias?	Yes	The WHO Composite International Diagnostic Interview (CIDI) was administered. The WHO Disability Assessment Scale (WHO-DAS; Buist-Bouwman et al. 2006) was used to determine days lost from work.

CASP Checklist for cohort studies			
			The occurrence (incidence or recurrence) of each disorder except headaches was examined for the periods before and after the accident and in the 12 months prior to interview.
5a	Have the authors identified all confounding factors?	Yes	Age in 1986, region, education, current employment status, current financial status, currently married, mental health prior to Chernobyl, and exposure.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Adjustments in analyses were made for age in 1986 and onset of disorder prior to 1986.
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	The clean-up workers were interviewed between December 2003 and June 2004, approximately 18 years after the accident.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	"Relatively more clean-up workers than controls experienced depression (18.0 % v. 13.1 %) and suicide ideation (9.2 % v. 4.1 %) after the accident. In the year preceding interview, the rates of depression (14.9 % v. 7.1 %), post-traumatic stress disorder (PTSD) (4.1 % v. 1.0 %) and headaches (69.2 % v. 12.4 %) were elevated. Affected workers lost more work days than affected controls. Exposure level was associated with current somatic and PTSD symptom severity" (p. 481).	
8	How precise are the results?	A p-value of less than 0.05 was considered significant.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	

CASP Checklist for cohort studies			
11	Do the results of this study fit with other available evidence?	Yes	With the evidence presented by these authors.
12	What are the implications of this study for practice?		This study is the first systematic investigation into the mental health of clean-up workers who participated in salvage activities after the Chernobyl disaster of 1986. Further study of this group is needed.

Loganovsky, Konstantyn, Iryna Perchuk, and Donatella Marazziti. 'Workers on Transformation of the Shelter Object of the Chernobyl Nuclear Power Plant into an Ecologically-Safe System Show QEEG Abnormalities and Cognitive Dysfunctions: A Follow-up Study'. *The World Journal of Biological Psychiatry* 17, no. 8 (2016): 600–607.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	"Investigate brain bioelectrical activity by qEEG, some cognitive functions through some neuropsychological tests, as well as psychiatric symptoms and/ or disorders, before and after working on the SO [shelter object] of the ChNPP [Chernobyl nuclear power plant]" (p. 601).
2	Was the cohort recruited in an acceptable way?	Yes	196 men, passed the preliminary medical tests and were eventually allowed to work at the SO, worked on the SO for between 7 and 42 months.
3	Was the exposure accurately measured to minimise bias?	Yes	Exposed to external irradiation at the dose range of 0–54.3 mSv, internal irradiation at the dose range of 0–2.4 mSv, total irradiation at the dose range of 0–56.7 mSv. "Depending on different previous contacts with sources of IR [ionising radiation], the surveyed subjects were divided into the following subgroups: subgroup A (clean-up workers of the Chernobyl accident, n=20); subgroup B (subjects who had been working in the nuclear industry, n=33); and subgroup C (subjects who had been working with the IR source, n= 143)" (p. 601).
4	Was the outcome accurately measured to minimise bias?	Yes	qEEG topographic mapping and four recognised neuropsychological and psychometric scales.
5a	Have the authors identified all confounding factors?	Can't tell	

CASP Checklist for cohort studies			
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Subjects had to pass medical testing prior to working on the SO, including screening out those with psychiatric or neurological disorders. Associations with smoking and alcohol are examined.
6a	Was the follow-up of subjects complete enough?	Yes	The examined subjects worked on the SO for between 7 and 42 months. They were assessed before (t0), and after (t1) working on the SO.
6b	Was the follow up of subjects long enough?	Can't tell	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	"At t1, the organized type of qEEG shifted towards the disorganized one" (p. 600). Neurocognitive tests revealed the presence of mild cognitive disorders at t1, for about 11 percent of subjects. "No specific psychiatric disorder was noted after working on the SO" (p. 605). "Taken together, the disturbances observed may be considered as cognitive symptoms of a chronic fatigue syndrome resulting from the exposure to ionizing radiation" (p. 600).	
8	How precise are the results?	A p-value of less than 0.05 was considered significant.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Note: the largest subgroup (n=143) with the most relevant qEEG changes had previous exposure to ionising radiation and exceeded limits of faecal transuranium elements.
11	Do the results of this study fit with other available evidence?	Yes	With other evidence presented by these authors.

CASP Checklist for cohort studies			
12	What are the implications of this study for practice?		"The most relevant qEEG changes were recorded in those workers exceeding the limits of faecal transuranium elements. Therefore, we hypothesize a synergistic role of duration of time working on the SO and the total radiation dose to determine changes in the frequency pattern of cerebral bioelectrical activity" (p. 605).

Milder, C., R. Sakata, H. Sugiyama, A. Sadakane, M. Utada, K. Cordova, A. Hida, W. Ohishi, K. Ozasa, and E. Grant. 'Initial Report for the Radiation Effects Research Foundation F1 Mail Survey'. *Asian Pacific Journal of Cancer Prevention : APJCP* 17, no. 3 (2016): 1313–23.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Cancer incidence and mortality from common adult diseases for children born to atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	One of the major cohorts being studied (F1).
3	Was the exposure accurately measured to minimise bias?	Can't tell	Discussion about the potential for social desirability responding.
4	Was the outcome accurately measured to minimise bias?	Yes	Self-reported outcomes.
5a	Have the authors identified all confounding factors?	Yes	Discussed a number of factors such as age and smoking.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Logistic and linear regression models accounted for common factors.
6a	Was the follow-up of subjects complete enough?	N/A	
6b	Was the follow up of subjects long enough?	N/A	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Little effect from exposure on outcome.	
8	How precise are the results?	Can't tell	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	

CASP Checklist for cohort studies			
11	Do the results of this study fit with other available evidence?	Yes	Results are consistent with previous studies.
12	What are the implications of this study for practice?		Further research is needed to follow this cohort.

Otake, M., W. J. Schull, and J. V. Neel. 'Congenital Malformations, Stillbirths, and Early Mortality among the Children of Atomic Bomb Survivors: A Reanalysis'. *Radiation Research* 122, no. 1 (1990): 1–11. https://doi.org/10.2307/3577576.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The study reanalysed the clinical data on survivors of the Hiroshima and Nagasaki atomic bombs from 1948-53, and focused on adverse pregnancy outcomes of this cohort.
2	Was the cohort recruited in an acceptable way?	Yes	The clinical records were from 55,303 participants in the ABCC study (which became the RERF).
3	Was the exposure accurately measured to minimise bias?	Yes	The authors converted the T65DR dosimetry measures in the clinical records into DS86 measures.
4	Was the outcome accurately measured to minimise bias?	Yes	The reported outcomes extracted from the clinical records are for congenital anomaly, stillborn birth or where the child died within 14 days of birth. The authors report that the clinical records covered 95 percent of pregnancies in the two cities lasting for at least 20 weeks of gestation and that infants were examined by a physician in the home and 30 percent were followed up at 8-10 months. An infant autopsy programme was also operating.
5a	Have the authors identified all confounding factors?	No	City, sex, mean age of father, mean age of mother, joint parental exposure, birth order of child, and year of birth were identified as potential confounding factors.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	A regression analysis was performed to address the confounding factors identified. No significant effects were found for city, sex, or age of mothers or fathers.
6a	Was the follow-up of subjects complete enough?	Yes	The clinical records were sourced from a long-term follow-up programme, the ABCC study.

CASP Checklist for cohort studies			
6b	Was the follow up of subjects long enough?	Yes	The clinical records were sourced from a long-term follow-up programme, the ABCC study.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	None of the models used in the analysis found a statistically significant effect of combined parental exposure, although all show that the risk for an untoward outcome of pregnancy increases with increasing dose.	
8	How precise are the results?	This is a reanalysis of clinical records and so is reliant on the accuracy of the records taken at the time.	
9	Do you believe the results?	Yes	The sample size is large and from a long-term cohort.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	Parents exposed to high-dose radiation who conceive after 5 years may still be at risk of increased complications from congenital abnormality, still birth, or the child dying in the first 2 weeks.
11	Do the results of this study fit with other available evidence?	Yes	Radiation is known to cause birth defects.
12	What are the implications of this study for practice?		For any parents who have been exposed to high-dose radiation in the previous 5 years before conception, the pregnancy should be monitored as they may be at increased risk of congenital abnormalities or still birth and the child should be closely monitored in the first weeks after birth.

Otani, K., M. Ohtaki, and H. Yasuda. 'Solid Cancer Mortality Risk among a Cohort of Hiroshima Early Entrants after the Atomic Bombing, 1970-2010: Implications Regarding Health Effects of Residual Radiation'. Journal of Radiation Research 63, no. 1 Supplement (2022): i45–53. **https://doi.org/10.1093/jrr/rrac036**

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Mortality risk from solid cancer and residual radiation from Hiroshima.
2	Was the cohort recruited in an acceptable way?	Yes	Used a registered database of atomic bomb survivors.
3	Was the exposure accurately measured to minimise bias?	Yes	Within 2km of the blast.
4	Was the outcome accurately measured to minimise bias?	Yes	From the Hiroshima prefectural governments.
5a	Have the authors identified all confounding factors?	Can't tell	
5b	Have they taken account of the confounding factors in the design and/or analysis?	Can't tell	
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	With adjustments for the age-dependent sensitivities to radiation exposure, it was extrapolated that middle-aged people who entered the city on the day of the bombing were exposed to higher levels of residual radiation than younger people.	
8	How precise are the results?	Can't tell	
9	Do you believe the results?	Can't tell	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Yes, fits with other evidence discussed.
12	What are the implications of this study for practice?		Not listed.

Parker, L., A. W. Craft, J. Smith, H. Dickinson, R. Wakeford, K. Binks, D. McElvenny, L. Scott, and A. Slovak. 'Geographical Distribution of Preconceptional Radiation Doses to Fathers Employed at the Sellafield Nuclear Installation, West Cumbria'. *British Medical Journal* 307, no. 6910 (1993): 966–71. https://doi.org/10.1136/bmj.307.6910.966.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Fathers' exposure to radiation and childhood risk of cancer.
2	Was the cohort recruited in an acceptable way?	Yes	Specific population.
3	Was the exposure accurately measured to minimise bias?	Yes	Monitoring data was used.
4	Was the outcome accurately measured to minimise bias?	Yes	Medical confirmation of diagnosis used.
5a	Have the authors identified all confounding factors?	No	Limited mention of confounding factors.
5b	Have they taken account of the confounding factors in the design and/or analysis?	No	Uncertain whether they have made adjustments in their analysis or design.
6a	Was the follow-up of subjects complete enough?	N/A	
6b	Was the follow up of subjects long enough?	N/A	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	No evidence of association.	
8	How precise are the results?	Uncertain, confounding is possible.	
9	Do you believe the results?	Can't tell	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	

CASP Checklist for cohort studies			
11	Do the results of this study fit with other available evidence?	Yes	Yes, with discussed evidence.
12	What are the implications of this study for practice?	Can’t tell	None listed or discussed.

Richardson, D. B., and G. Hamra. 'Ionizing Radiation and Kidney Cancer among Japanese Atomic Bomb Survivors'. *Radiation Research* 173, no. 6 (2010): 837–42. https://doi.org/10.1667/RR2096.1.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Association between ionising radiation dose and cancer of the renal pelvis and ureters and cancer of the renal parenchyma using cancer incidence from the LSS.
2	Was the cohort recruited in an acceptable way?	Yes	LSS.
3	Was the exposure accurately measured to 136inimize bias?	Yes	LSS.
4	Was the outcome accurately measured to 136inimize bias?	Yes	LSS.
5a	Have the authors identified all confounding factors?	Yes	
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Sex, city, attained age, age at exposure, and location.
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	1 Jan 1958 to 31 December 1998.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Positive association identified.	
8	How precise are the results?	Confidence intervals included.	
9	Do you believe the results?	Yes	Much larger sample size than previous similar studies.
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?	Can't tell	

Roman, E., P. Doyle, N. Maconochie, G. Davies, P. G. Smith, and V. Beral. 'Cancer in Children of Nuclear Industry Employees: Report on Children Aged under 25 Years from Nuclear Industry Family Study'. *British Medical Journal* 318, no. 7196 (1999): 1443–50. https://doi.org/10.1136/bmj.318.7196.1443.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	To determine whether children of men and women occupationally exposed to ionising radiation are at increased risk of developing leukaemia or other cancers before their 25th birthday.
2	Was the cohort recruited in an acceptable way?	Yes	Children of workers.
3	Was the exposure accurately measured to minimise bias?	Yes	Radiation dose is measured as part of employment.
4	Was the outcome accurately measured to minimise bias?	Yes	Medical confirmation.
5a	Have the authors identified all confounding factors?	Can't tell	Unclear if they have adjusted.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Can't tell	
6a	Was the follow-up of subjects complete enough?	N/A	
6b	Was the follow up of subjects long enough?	N/A	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	The observed number of cases of leukaemia in the exposed population were similar to the expected number of cases based on national rates for England and Wales.	
8	How precise are the results?	Accurate.	
9	Do you believe the results?	Yes	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Aligns with other evidence.
12	What are the implications of this study for practice?		That children of nuclear workers are not at an increased risk of developing cancer before the age of 25.

Semmens, E. O., K. J. Kopecky, E. Grant, R. W. Mathes, N. Nishi, H. Sugiyama, H. Moriwaki, et al. 'Relationship between Anthropometric Factors, Radiation Exposure, and Colon Cancer Incidence in the Life Span Study Cohort of Atomic Bomb Survivors'. *Cancer Causes and Control* 24, no. 1 (2013): 27–37. https://doi.org/10.1007/s10552-012-0086-8.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Association between excess body weight and colon cancer risk in atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	LSS.
3	Was the exposure accurately measured to minimise bias?	Yes	LSS.
4	Was the outcome accurately measured to minimise bias?	Yes	LSS.
5a	Have the authors identified all confounding factors?	Yes	Anthropometric variables e.g., body mass index and height.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	Follow-up to 2002.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Body mass index did not significantly influence the relationship between radiation dose and colon cancer risk.	
8	How precise are the results?	Confidence intervals included.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Yes	Most (but not all) of the sample were exposed as adults.
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?	Can’t tell	

Shimizu, Y., K. Kodama, N. Nishi, F. Kasagi, A. Suyama, M. Soda, E. J. Grant, et al. 'Radiation Exposure and Circulatory Disease Risk: Hiroshima and Nagasaki Atomic Bomb Survivor Data, 1950-2003'. *BMJ (Online)* 340, no. 7739 (2010): 193. https://doi.org/10.1136/bmj.b5349.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	To investigate the degree to which ionising radiation confers risk of mortality from heart disease and stroke.
2	Was the cohort recruited in an acceptable way?	Yes	LSS cohort.
3	Was the exposure accurately measured to minimise bias?	Yes	Based on distance.
4	Was the outcome accurately measured to minimise bias?	Yes	Medical diagnosis.
5a	Have the authors identified all confounding factors?	Yes	Identified and adjusted for potential confounders.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	As above.
6a	Was the follow-up of subjects complete enough?	Yes	
6b	Was the follow up of subjects long enough?	Yes	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Doses above 0.5 Gy are associated with an elevated risk of both stroke and heart disease, but the degree of risk at lower doses is unclear.	
8	How precise are the results?	Precise.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Fits with other evidence discussed.
12	What are the implications of this study for practice?		This study provides the strongest evidence available to date that radiation may increase the rates of stroke and heart disease at moderate dose levels (mainly 0.5-2 Gy), but robust confirmatory evidence from other studies is needed.

Taguchi, M., H. Mishima, Y. Shiozawa, C. Hayashida, A. Kinoshita, Y. Nannya, H. Makishima, et al. 'Genome Analysis of Myelodysplastic Syndromes among Atomic Bomb Sur Vivors in Nagasaki'. *Haematologica* 105, no. 2 (2020): 358–65. https://doi.org/10.3324/haematol.2019.219386.

CASP Checklist for case control studies			
Section A: Are the results of the trial valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The study focused on genome analyses of MDS among atomic bomb survivors in Nagasaki.
2	Did the paper use an appropriate method to answer their question?	Yes	They identified genomic changes using standard approaches – next generation sequencing and single nucleotide polymorphism analysis.
3	Were the cases recruited in an acceptable way?	No	They analysed samples from 32 atomic bomb survivors with MDS diagnosed at Nagasaki University Hospital and Sasebo City General Hospital. The samples were collected from 1995 to 2015. There may be bias in the sample due to the small sample size and location specific sampling.
4	Were the controls selected in an acceptable way?	Yes	The 32 atomic bomb survivors were divided into two groups: - those within 2.7 km of the hypocentre (Proximal Exposure) - and those between 2.7 and 10km of the hypocentre (Distal Exposure). The Proximal Exposure group was compared to the Distal Exposure groups as the dose of atomic bomb radiation in the Distal Exposure group was estimated to be less than 0.005 Gy.

CASP Checklist for case control studies			
			The authors state there "were no significant differences in the sex, subtype of MDS, age at diagnosis, or age at the time of the bombing between the two groups" (p. 359).
5	Was the exposure accurately measured to minimise bias?	Can't tell	The study used samples collected from atomic bomb survivors with MDS between 1995 and 2015, so there were no direct measurements of exposure but a standard definition of exposure was used from the RERF. They estimated the dose of atomic bomb radiation for those within 2.7 km of the hypocentre to be between 9.8 and 0.005 Gy according to the dosimetry system DS02.
6(a)	Aside from the experimental intervention, were the groups treated equally?	N/A	This was a study of samples.
6(b)	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Can't tell	The authors compared the Proximal Exposure and Distal Exposure groups "because these two groups would have lived in similar circumstances (stayed in Nagasaki after A-bomb under similar environmental circumstances including medical access) except for the dose of A-bomb radiation, more than 5 mGy (at 2.7 km) or less" (p. 359).
Section B: What are the results?		**Comments**	
7	How large was the treatment effect?	Significant differences were found in the profile of mutated genes between proximally and distally exposed patients' samples and that further study is required to understand how these genetic alterations after radiation exposure contribute to the development of myelodysplastic syndromes.	
8	How precise was the estimate of the treatment effect?	Statistically significant differences were found for some genome changes e.g., copy number loss for 11q in the Proximal Exposure group.	
9	Do you believe the results?	Yes	The sample size is small, meaning that further investigation is required to assess how robust the

CASP Checklist for case control studies			
			associations are. The applicability may also limited, as the samples were only from those exposed to an atomic bomb and subsequently developed MDS.
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
10	Can the results be applied to the local population?	Can't tell	This would only apply to people that were within 2.7km of the hypocentre of an atomic bomb detonation and subsequently developed MDS.
11	Do the results fit with other available evidence?	Yes	Exposure to radiation has been shown to cause genomic changes in other studies.

Takahashi, I., R. D. Abbott, T. Ohshita, T. Takahashi, K. Ozasa, M. Akahoshi, S. Fujiwara, K. Kodama, and M. Matsumoto. 'A Prospective Follow-up Study of the Association of Radiation Exposure with Fatal and Non-Fatal Stroke among Atomic Bomb Survivors in Hiroshima and Nagasaki (1980-2003)'. *BMJ Open* 2, no. 1 (2012). https://doi.org/10.1136/bmjopen-2011-000654.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	The purpose of this study was to examine the association between radiation exposure and the incidence of stroke among Japanese atomic bomb survivors.
2	Was the cohort recruited in an acceptable way?	Yes	LSS cohort.
3	Was the exposure accurately measured to minimise bias?	Yes	LSS cohort.
4	Was the outcome accurately measured to minimise bias?	Yes	Medical diagnosis.
5a	Have the authors identified all confounding factors?	Yes	Discussed the common risk factors for stroke.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Adjusted for common factors.
6a	Was the follow-up of subjects complete enough?	Yes	24 years.
6b	Was the follow up of subjects long enough?	Yes	24 years.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Increased risk of one form of stroke for women as radiation dose increase.	
8	How precise are the results?	Well conducted study.	
9	Do you believe the results?	Yes.	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**

CASP Checklist for cohort studies			
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Yes, fits with evidence.
12	What are the implications of this study for practice?		Potential that radiotherapy exposure could increase the risk of stroke later in life.

Yamada, M., H. Sasaki, F. Kasagi, M. Akahoshi, Y. Mimori, K. Kodama, and S. Fujiwara. 'Study of Cognitive Function among the Adult Health Study (AHS) Population in Hiroshima and Nagasaki'. *Radiation Research* 158, no. 2 (2002): 236–40. https://doi.org/10.1667/0033-7587(2002)158[0236:SOCFAT]2.0.CO;2.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	"Examined the effects of A-bomb radiation exposure on cognitive function among adult survivors in the Adult Health Study (AHS)" (p. 236).
2	Was the cohort recruited in an acceptable way?	Yes	AHS cohort, a subsample of the LSS. Included 20,000 subjects at inception and comprised four groups matched for city, age, and sex. Men and women born prior to September 1932 who had undergone biennial examinations during the period 1992-1996 in Hiroshima or 1993-1998 in Nagasaki.
3	Was the exposure accurately measured to minimise bias?	Yes	"We used the DS86 dosimetry system of truncating the maximum dose at 6 Gy to estimate radiation dose…The study included 1,099 subjects with 0mGy exposure and 506 with unknown exposure. Doses had been computed for 1,120 subjects in Hiroshima (mean dose=748 mGy) and 388 in Nagasaki (mean dose=1,035 mGy)" (p. 237).
4	Was the outcome accurately measured to minimise bias?	Yes	Cognitive performance for 3,113 subjects with the Cognitive Abilities Screening Instrument (CASI). CASI consists of 10 cognitive domains including attention, memory, and language. "Examined the relationship between cognitive performance and potentially related factors (sex, age, city where the subjects were exposed, years of education, and radiation dose)" (p. 236).

CASP Checklist for cohort studies			
5a	Have the authors identified all confounding factors?	Yes	See (4) above.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	These were accounted for in the regression analyses.
6a	Was the follow-up of subjects complete enough?	Yes	Approximately one half of the cohort died before 1992, and a smaller number moved away or refused to participate. But about 6000 continue to participate. This study examined 2,052 subjects in Hiroshima, and 1,065 in Nagasaki. The percentage of those who refused cognitive testing and percentage of fully examined subjects did not differ by radiation dose.
6b	Was the follow up of subjects long enough?	Yes	> 45 years since Hiroshima and Nagasaki.
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	"In contrast to exposure to radiotherapy, exposure to atomic bomb radiation had no apparent effect on cognitive function. Factors that did affect cognitive function were age, sex, city and years of education" (p. 236). No association between incidence or mortality from stroke among irradiated survivors and enhanced decline of cognitive function. No evidence of a radiation effect on the prevalence of any type of dementia.	
8	How precise are the results?	A p-value of less than 0.05 was considered significant.	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	

CASP Checklist for cohort studies			
11	Do the results of this study fit with other available evidence?	Can’t tell	“This is the first investigation into the relationship between neurological (cognitive) function and radiation exposure in mature A-bomb survivors” (p. 239).
12	What are the implications of this study for practice?		“Neurological functions other than cognitive function, such as reaction time, should be evaluated before a final conclusion is reached” (p. 239).

Yamada, M., F. Kasagi, Y. Mimori, T. Miyachi, T. Ohshita, and H. Sasaki. 'Incidence of Dementia among Atomic-Bomb Survivors - Radiation Effects Research Foundation Adult Health Study'. *Journal of the Neurological Sciences* 281, no. 1–2 (2009): 11–14. https://doi.org/10.1016/j.jns.2009.03.003.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Examined whether exposure to atomic bomb radiation affected the incidence of dementia among 2,286 atomic bomb survivors and controls — all members of the AHS cohort.
2	Was the cohort recruited in an acceptable way?	Yes	AHS cohort.
3	Was the exposure accurately measured to minimise bias?	Yes	Three levels of exposure.
4	Was the outcome accurately measured to minimise bias?	Yes	Medical diagnosis.
5a	Have the authors identified all confounding factors?	Can't tell	
5b	Have they taken account of the confounding factors in the design and/or analysis?	Yes	Adjusted for many common confounders.
6a	Was the follow-up of subjects complete enough?	N/A	
6b	Was the follow up of subjects long enough?	N/A	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Radiation exposure was not a risk factor for dementia among atomic bomb survivors exposed after they were 13 years old.	
8	How precise are the results?		
9	Do you believe the results?	Can't tell	

CASP Checklist for cohort studies			
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	Fits with available evidence.
12	What are the implications of this study for practice?		Future examination will be required to determine neurological sequelae among atomic survivors exposed at <13 years of age.

Yamada, M., K. Furukawa, Y. Tatsukawa, K. Marumo, S. Funamoto, R. Sakata, K. Ozasa, H. M. Cullings, D. L. Preston, and P. Kurttio. 'Congenital Malformations and Perinatal Deaths Among the Children of Atomic Bomb Survivors: A Reappraisal'. *American Journal of Epidemiology* 190, no. 11 (2021): 2323–33. https://doi.org/10.1093/aje/kwab099.

CASP Checklist for cohort studies			
Section A: Are the results of the study valid?		**Yes/Can't tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	"Reexamined the risk of major congenital malformations and perinatal deaths in the offspring of the atomic bomb survivors" (p. 2,324).
2	Was the cohort recruited in an acceptable way?	Yes	ABCC / RERF large-scale study of pregnancy outcomes between 1948-1954. 71,603 births included.
3	Was the exposure accurately measured to minimise bias?	Can't tell	Used a different method on data from a previous study to estimate radiation dose.
4	Was the outcome accurately measured to minimise bias?	Yes	Soon after delivery of a baby, midwives and physicians collected information on the pregnancy.
5a	Have the authors identified all confounding factors?	Can't tell	They have discussed some factors and other potential biases.
5b	Have they taken account of the confounding factors in the design and/or analysis?	Can't tell	
6a	Was the follow-up of subjects complete enough?	N/A	
6b	Was the follow up of subjects long enough?	N/A	
Section B: What are the results of this study?		**Comments**	
7	What are the results of this study?	Overall, this study did not find any statistically significant associations that indicate that the offspring included in this study were at a greater risk of major congenital malformations or perinatal deaths.	

CASP Checklist for cohort studies			
8	How precise are the results?	Can't tell	
9	Do you believe the results?	Yes	
Section C: Can the results help locally?		**Yes/Can't Tell/No**	**Comments**
10	Can the results be applied to the local population?	Yes	
11	Do the results of this study fit with other available evidence?	Yes	
12	What are the implications of this study for practice?		May be useful for risk assessment purposes.

Appendix C: Critical appraisals for case control studies

Case control studies were appraised for quality using the CASP Case Control Study checklist.[62]

Horai, M., H. Mishima, C. Hayashida, A. Kinoshita, Y. Nakane, T. Matsuo, K. Tsuruda, et al. 'Detection of de Novo Single Nucleotide Variants in Offspring of Atomic-Bomb Survivors Close to the Hypocenter by Whole-Genome Sequencing'. *Journal of Human Genetics* 63, no. 3 (2018): 357–63. https://doi.org/10.1038/s10038-017-0392-9.

CASP Checklist for case control studies			
Section A: Are the results of the trial valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	De novo variants in offspring of atomic bomb survivors.
2	Did the paper use an appropriate method to answer their question?	Yes	Very complex method used.
3	Were the cases recruited in an acceptable way?	Yes	Recruited from a cohort of individuals who have regular health check-ups at the Nagasaki Atomic Bomb Casualty Council Health Management Center.
4	Were the controls selected in an acceptable way?	N/A	Used non exposed blood samples.
5	Was the exposure accurately measured to minimise bias?	Yes	Yes, survivors with acute radiation symptoms.
6(a)	Aside from the experimental intervention, were the groups treated equally?		
6(b)	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Can't tell	Not clear what they have done for this.
Section B: What are the results?		**Comments**	

[62] Checklist available at https://casp-uk.net/images/checklist/documents/CASP-Case-Control-Study-Checklist/CASP-Case-Control-Study-Checklist-2018-fillable-form.pdf

CASP Checklist for case control studies			
7	How large was the treatment effect?	N/A	
8	How precise was the estimate of the treatment effect?	N/A	
9	Do you believe the results?	Yes	Fits with other evidence discussed.
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
10	Can the results be applied to the local population?	Yes	
11	Do the results fit with other available evidence?	Yes	Identified and discussed other study data.

Livshits, L. A., S. G. Malyarchuk, E. M. Lukyanova, Y. G. Antipkin, L. P. Arabskaya, S. A. Kravchenko, G. H. Matsuka, et al. 'Children of Chernobyl Cleanup Workers Do Not Show Elevated Rates of Mutations in Minisatellite Alleles'. *Radiation Research* 155, no. 1 (2001): 74–80. https://doi.org/10.1667/0033-7587(2001)155[0074:COCCWD]2.0.CO;2.

CASP Checklist for case control studies			
Section A: Are the results of the trial valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Measure inherited allele mutations in the children of Chernobyl workers.
2	Did the paper use an appropriate method to answer their question?	Yes	Used blood and DNA extraction and analysis.
3	Were the cases recruited in an acceptable way?	Yes	All families from Kiev with fathers who worked at the Chernobyl plant.
4	Were the controls selected in an acceptable way?	Yes	Recruited from other regions of Ukraine with no exposures.
5	Was the exposure accurately measured to minimise bias?	Yes	Exposure was considered presence at the plant but not specifically measured.
6(a)	Aside from the experimental intervention, were the groups treated equally?	Yes	
6(b)	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Can't tell	No factors listed, uncertain of relevance for this type of study.
Section B: What are the results?		**Comments**	
7	How large was the treatment effect?	N/A	
8	How precise was the estimate of the treatment effect?	N/A	
9	Do you believe the results?	Yes	Fits with other available evidence.

CASP Checklist for case control studies			
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
10	Can the results be applied to the local population?	Yes	
11	Do the results fit with other available evidence?	Yes	Fits with other available evidence.

Loganovsky, K. N., and K. L. Yuryev. 'EEG Patterns in Persons Exposed to Ionizing Radiation as a Result of the Chernobyl Accident: Part 1: Conventional EEG Analysis'. *Journal of Neuropsychiatry and Clinical Neurosciences* 13, no. 4 (2001): 441–58. https://doi.org/10.1176/jnp.13.4.441.

CASP Checklist for case control studies			
Section A: Are the results of the trial valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	"Prospective characterization of brain electrical activity by conventional EEG in Chernobyl accident survivors who had been exposed to ionising radiation, in order to test the hypotheses that the following would be found: 1) specificity of neurophysiological abnormalities in irradiated patients that can be considered as radiation effects on the brain, and 2) possible dose-related neurophysiological effects of ionizing radiation" (p. 442).
2	Did the paper use an appropriate method to answer their question?	Yes	
3	Were the cases recruited in an acceptable way?	Yes	Patients who had acute radiation sickness and emergency workers in 1986 ("liquidators"). I—ARS patients (dose more than 1 Gy), and II—liquidators (0.1–1 Gy). N=64, and n= 80 at stage 2, respectively.
4	Were the controls selected in an acceptable way?	Yes	Control groups comprised healthy volunteers; veterans of the Afghanistan war with posttraumatic stress disorder; veterans with mild traumatic brain injury; and patients with dyscirculatory encephalopathy. n=15, n=21, n=22, n=20 at stage 2, respectively. All groups exposed to background radiation only.
5	Was the exposure accurately measured to 160inimize bias?	Yes	ARS – "Their absorbed dose of whole-body irradiation was 1–6 Gy (2.11.1 Gy). Dosimetrical assessment of ARS patients was provided by the Department of Dosimetry and Radiation Hygiene of RCRM, Kiev, and was also

CASP Checklist for case control studies			
			supported by the data of cytogenetic dosimetry provided by the Institute of Biophysics, Moscow, in 1986" (p. 444). Liquidators – "Their absorbed dose of whole-body irradiation was 0.10.99 Gy (0.40.2 Gy). Dosimetrical assessment of ARS patients was provided by RCRM" (p. 445.)
6(a)	Aside from the experimental intervention, were the groups treated equally?	Yes	
6(b)	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes	Participants were excluded on the basis of several potential confounding factors, for instance, any mental, neurological, and/or physical disease or head trauma, meeting ICD-10 criteria for current or past dependence on alcohol, marijuana, or any psychoactive substances (other than tobacco).
Section B: What are the results?		**Comments**	
7	How large was the treatment effect?	H1: "At 3–5 years after irradiation, ARS patients compared with liquidators had lower amplitude of beta activity, and in the later period they had less paroxysmal and alpha activity as well as more reactive EEG patterns" (p. 456). H2: "However, we cannot reveal a statistically significant dose–effect relationship concerning conventional EEG parameters" (p. 456).	
8	How precise was the estimate of the treatment effect?	A p-value of less than 0.05 was considered significant.	
9	Do you believe the results?	Yes	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
10	Can the results be applied to the local population?	Yes	

CASP Checklist for case control studies			
11	Do the results fit with other available evidence?	Yes	With other evidence outlined by these authors.

Moorhouse, A. J., M. Scholze, N. Sylvius, C. Gillham, C. Rake, J. Peto, R. Anderson, and Y. E. Dubrova. 'No Evidence of Increased Mutations in the Germline of a Group of British Nuclear Test Veterans'. *Scientific Reports* 12, no. 1 (2022). https://doi.org/10.1038/s41598-022-14999-w.

CASP Checklist for case control studies			
Section A: Are the results of the trial valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	Germline mutations in families of UK test veterans.
2	Did the paper use an appropriate method to answer their question?	Yes	Yes, blood sampling and DNA analysis used.
3	Were the cases recruited in an acceptable way?	Yes	Blood samples obtained from the Genetic and Cytogenetic Family Trio study.
4	Were the controls selected in an acceptable way?	Yes	Matched on age, service, and period of service.
5	Was the exposure accurately measured to minimise bias?	Yes	Yes, dose estimates based on role and distance to blast.
6(a)	Aside from the experimental intervention, were the groups treated equally?	Yes	
6(b)	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes	Addressed small sample size.
Section B: What are the results?		**Comments**	
7	How large was the treatment effect?	No effect	
8	How precise was the estimate of the treatment effect?	Accurate	
9	Do you believe the results?	Yes	Aligned with other evidence presented.
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
10	Can the results be applied to the local population?	Yes	

CASP Checklist for case control studies			
11	Do the results fit with other available evidence?	Yes	As above.

Remennick, L. I. 'Immigrants from Chernobyl-Affected Areas in Israel: The Link between Health and Social Adjustment'. *Social Science and Medicine* 54, no. 2 (2002): 309–17. https://doi.org/10.1016/S0277-9536(01)00030-2.

CASP Checklist for case control studies			
Section A: Are the results of the trial valid?		**Yes/Can't Tell/No**	**Comments**
1	Did the study address a clearly focused issue?	Yes	"The current study addressed the influence of perceived somatic and mental health status on the immigration experience, social adjustment and general well-being of Chernobyl survivors in Israel" (p. 311).
2	Did the paper use an appropriate method to answer their question?	Yes	A semi-structured questionnaire was specially developed for this study, drawing on seven in-depth interviews with Chernobyl survivors and on the earlier research on stress-related disorders among this group. 20 percent of questions were open-ended (qualitative). Social adjustment rather than psychopathology.
3	Were the cases recruited in an acceptable way?	Yes	Post-1989 Russian immigrants of working age (30–59): 180 persons who came from Chernobyl-affected areas. Recruited via snowballing that was started by Chernobyl advocacy organisations.
4	Were the controls selected in an acceptable way?	Yes	Post-1989 Russian immigrants of working age (30–59): 200 persons from other areas of the former Soviet Union. Contacted in different places of immigrants' gathering-retraining courses, shopping and entertainment centers, school meetings, etc.
5	Was the exposure accurately measured to minimise bias?	Can't tell	Used the list of Soviet cities and towns with established levels of radio-contamination (IAEA, 1991) as an eligibility criterion.
6(a)	Aside from the experimental intervention, were the groups treated equally?	Yes	

CASP Checklist for case control studies			
6(b)	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes	Age, gender, marital status, tenure in Israel, education, and current occupation.
Section B: What are the results?		**Comments**	
7	How large was the treatment effect?	"Both the somatic and mental health of Chernobyl survivors were significantly worse than in other immigrants of the same gender and age; a significant share of reported health problems were probably psychosomatic. Depression, sense of stigma and cancer-related anxiety were more prevalent in the study group. Immigrants from contaminated areas tended to use more health services (both conventional and alternative), but were less satisfied with their quality and providers' attitude" (p. 309). Univariate and multivariate odds ratios for 5 out of 7 outcome measures of health status and health care use are (statistically significant) above 1.0, with 2 out of 7 outcome measures above 3.0.	
8	How precise was the estimate of the treatment effect?	A p-value of less than 0.05 was considered significant.	
9	Do you believe the results?	Yes	
Section C: Will the results help locally?		**Yes/Can't Tell/No**	
10	Can the results be applied to the local population?	Can't tell	The case sample is comprised of radiation survivors who immigrated, and this may impact the generalisability of the results. In particular due to the concept of 'cumulative adversity'.
11	Do the results fit with other available evidence?	Can't tell	

Appendix D: Critical appraisals for qualitative studies

Qualitative studies were appraised for quality using the CASP Checklist for Qualitative research checklist.[63]

Murphy, B. C., P. Ellis, and S. Greenberg. 'ATOMIC VETERANS AND THEIR FAMILIES: Responses to Radiation Exposure'. *American Journal of Orthopsychiatry* 60, no. 3 (1990): 418–27. https://doi.org/10.1037/h0079182.

CASP Checklist for Qualitative research			
Section A: Are the results valid?		**Yes/Can't Tell/No**	**Comments**
1	Was there a clear statement of the aims of the research?	Yes	"Explores not only the responses of atomic veterans to the radiation exposure, but also the effects of the veterans' experiences on their families" (p. 419).
2	Is a qualitative methodology appropriate?	Yes	
3	Was the research design appropriate to address the aims of the research??	Yes	Semi-structured, videotaped interviews. There were always at least two members of the team present, enabling interviewers to monitor and shape the interview.
4	Was the recruitment strategy appropriate to the aims of the research?	Yes	Atomic veterans, located via a member of the Massachusetts Chapter of National Association of Atomic Veterans. "Of the seven veterans interviewed, three had participated in atomic testing in the Pacific, and three in Nevada; one had participated in the clean-up of Hiroshima" (p. 420). Of the seven veterans interviewed, three included their wives and children in the interviews, subsequently a total of 17 members of atomic veteran families participated.

[63] Checklist available at https://casp-uk.net/images/checklist/documents/CASP-Qualitative-Studies-Checklist/CASP-Qualitative-Checklist-2018_fillable_form.pdf

CASP Checklist for Qualitative research			
5	Was the data collected in a way that addressed the research issue??	Yes	See (3) above. "Our collaborative model meant that we included the families as consultants to the project" (p. 426).
6	Has the relationship between researcher and participants been adequately considered?	Yes	The collaborative model meant that families were involved in modifying the interview, interpreting the results, and suggesting future areas of exploration.
Section B: What are the results?		**Yes/Can't Tell/No**	**Comments**
7	Have ethical issues been taken into consideration?	Can't tell	No detail regarding ethics applications or other ethical issues.
8	Was the data analysis sufficiently rigorous?	Can't tell	Data analysis not described in detail.
9	Is there a clear statement of findings?	Yes	"Our interviews with seven atomic veterans and their families indicate that exposure to low level ionizing radiation has powerful psychological effects on all members of the family" (p. 426). "Four themes emerged: the invalidation of their experiences by government and other authority figures; family concerns about genetic effects on future generations; family members' desire to protect each other from fears of physical consequences; and desire to leave a record of their experiences to help prevent future suffering" (p. 418).
Section C: Will the results help locally?		**Comments**	
10	How valuable is the research?	Exploratory study. Discusses contribution to existing understanding. "The themes that emerged from these interviews with atomic veterans and their families dovetail with those of other studies of comparable populations" (p. 423).	

CASP Checklist for Qualitative research		
		Does not identify next steps for research. “The current findings may suggest strategies for intervention and support on behalf of others coping with actual or potential nuclear injury, as well as those exposed to a range of similar experiences” (p. 426).

ALLEN + CLARKE

+64 4 890 7300

office@allenandclarke.co.nz

www.allenandclarke.co.nz