Review paper

**Cancer risk following low doses of ionising radiation – current epidemiological evidence and implications for radiological protection**

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**Abstract**

Recent studies suggest that every year worldwide about a million patients might be exposed to doses of the order of 100 mGy of low-LET radiation, due to recurrent application of radioimaging procedures. This paper presents a synthesis of recent epidemiological evidence on radiation-related cancer risks from low-LET radiation doses of this magnitude. Evidence from pooled analyses and meta-analyses involving epidemiological studies that, individually, do not find statistically significant radiation-related cancer risks is reviewed, and evidence from additional and more recent epidemiological studies of radiation exposures indicating excess cancer risks is also summarized. Cohorts discussed in the present paper include Japanese atomic bomb survivors, nuclear workers, patients exposed for diagnostic or therapeutic purposes, and populations exposed environmentally to natural background radiation or radioactive contamination. Taken together, the overall evidence summarized here is based on studies including several million individuals, many of them followed-up for more than half a century.

Results from the atomic bomb survivors indicate significant radiation-related effects at weighted doses greater than 100 mGy, for leukaemia, all solid cancers combined and for a number of specific solid cancer sites. For all solid cancers combined, a significant radiation-related risk was found even when data were restricted to survivors with weighted colon doses of less than 100 mGy. Studies of nuclear workers from the UK and the Russian Mayak installation and of Chernobyl clean-up workers, who were exposed to low dose rates, all show significant radiation-related cancer risks for cumulative radiation doses greater than 100 mGy. In a pooled study of nuclear workers from the US, France and the UK, a significant radiation-related risk for all solid cancers combined was found when data were restricted to workers with cumulative doses of less than 100 mGy, also found in the most recent follow-up of UK nuclear workers. Evidence for an increased radiation-related solid cancer risk was also found in some environmentally exposed cohorts such as the Techa River population in the Southern Urals, Russia. Case-control studies of childhood cancer have found consistent associations with an antenatal X-ray examination, and recent cohort studies of children exposed during CT scanning have found evidence of raised risks of leukaemia and brain tumours.

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 acute and protracted 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 small doses accumulated over many years at low dose rates do cause stochastic health effects. On this basis, it can be concluded that doses of the order of 100 mGy from recurrent application of medical imaging procedures involving ionizing radiation are of concern, from the viewpoint of radiological protection.

**Introduction**

**Setting the Scene**

Since its discovery by Wilhelm Conrad Röntgen in 1895, ionizing radiation has been widely used in medical settings either in radiotherapy or in diagnostics. One of the first applications used by Röntgen – an image of the hand of his wife – demonstrated the great potential of his discovery, i.e., to visualize structures within the human body without any need to involve surgical interventions. Since then, application of X-rays in medical imaging has been continuously growing worldwide, and is today an indispensable part of modern health care systems.

By way of example, according to the most recent review of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the number of computed tomography (CT) procedures in the United States increased from about 20 million in 1993 to more than 60 million in 2006, an average increase of more than 10% per year, with a steeper increase of about 17% since 1998 (UNSCEAR 2010). More recently, in Germany, the frequency of CT examinations per inhabitant and year continuously increased from about 0.105 in 2007 to 0.145 in 2015. This led to an increase in mean effective dose per person-year from 0.8 mSv in 2007 to 1.0 mSv in 2015 (page 95) (BfS 2017). However, while such numbers demonstrate the increasing importance of CT procedures in medical imaging, they do not detail the dose received by individual patients from multiple CT scans.

Recently, Rehani and co-workers investigated those patients undergoing multiple CT procedures and whether such patients might be exposed to cumulative radiation doses that are of concern in terms of radiation-related cancer risk. In their study, Rehani et al. used data from four institutions in the US including more than 300 hospitals. Based on the radiation dose monitoring systems used at these institutions they identified more than 2.5 million patients with about 4.8 million CT exams received within a period of between one and five years. More than 1% of these patients (i.e., more than 33,000 patients) were exposed to cumulated effective doses of more than 100 mSv. Median cumulated effective dose was 130 mSv and the maximum effective dose found was almost 1,200 mSv. Although most of these patients were older than 50 years, a significant fraction of almost 20% was younger (Rehani et al. 2019). These findings have prompted the International Atomic Energy Agency to organize a meeting with participants from 26 countries including experts in various relevant scientific disciplines and representatives of international organisations. The conclusion of this meeting was that it might well be that globally almost one million patients per year are exposed to cumulative effective doses of more than 100 mSv (Brambilla et al. 2020). Thus, doses from CT imaging procedures require further attention (Rühm et al. 2020).

**Evolution of the definition of low doses**

Up to the 1950s, radiation protection considered only occupational exposures and was intended to protect against short-term acute effects of radiation (ICRP 109, 2009; Taylor, 2002 ; Clarke, 2005). The concept of stochastic effects, for which the probability of occurrence rather than severity varies with dose, was introduced in ICRP Publication 9 in 1966. Then, the question of defining a dose threshold for these stochastic effects, especially leukemia and solid cancers, occurred. ICRP stated that “*The mechanism of the induction by radiation of leukaemia and other types of malignancy is not known. Such induction has so far been clearly established after doses of more than 100 rads (1 Gy), but it is unknown whether a threshold dose exists below which no malignancy is produced. If such a threshold dose did exist, there would be no risk of the induction of malignancy, as long as the threshold was not exceeded. As the existence of a threshold dose is unknown, it has been assumed that even the smallest doses involve a proportionately small risk of induction of malignancies.*” (ICRP Pub 9, 1966)

Twenty-five years later, in 1991, ICRP analysed the level of dose for which risks are discernible in the following way – “*The principal source of risk estimation to be discussed later will be the Japanese survivors of the atomic bombs who were exposed to a range of doses at high dose rate and in whom statistically significant excess of cancer have been observed at doses down to 0.2 Gy*”. On this basis and based on theoretical considerations, experimental results in animals and other biological organisms, the ICRP proposed a range of absorbed doses below 0.2 Gy (and dose rate less than 0.1 Gy per hour for higher doses) the application of a reduction factor denominated the Dose and Dose Rate Effectiveness Factor (DDREF) (ICRP Publication 60, 1991).

Shortly after 2000, emerging results with regard to radiation-related adaptive responses, genomic instability, and bystander eﬀects suggested that the risk of low-level exposure to ionising radiation was uncertain, and a simple extrapolation from high-level exposure eﬀects may not be wholly justiﬁed in all instances. The French Academies report concluded that the LNT model and its use for assessing the risks associated with low doses was not based on scientific evidence (Tubiana 2005). In contrast, the US Committee on the Biological Effects of Ionizing Radiations (BEIR) Seventh Report (NRC 2006) recommended the use of the LNT model. Some authors considered that “*For low linear energy transfer radiation, experimental animal data show the absence of carcinogenic effects for acute irradiation at doses less than 100 mSv and for chronic irradiation at doses less than 500 Sv. Among humans, there is no evidence of a carcinogenic effect for acute irradiation at doses less than 100 mSv and for protracted irradiation at doses less than 500 mSv*” (Tubiana et al 2009). In 2007, Tubiana et al. stated that for doses above about 200 mSv, epidemiological data allow the dose-response relationship to be assessed with relatively high precision. However, for low doses, and even more so for very low doses, epidemiology can neither affirm the existence of an excess of cancer, nor exclude the possibility of it. However, it shows that this risk, if it exists, is low. These studies detect no effect for doses lower than about 100-200 mSv in adults and 80-100 mSv in children, either because there is no effect or because the statistical power of the surveys was insufficient to detect them (Tubiana et al, 2007).

At the same time, ICRP conducted a detailed review of the scientific literature and performed a formal quantitative uncertainty analysis of the dose-risk relationship at low doses. The report concludes that “*while existence of a low-dose threshold does not seem to be unlikely for radiation-related cancers of certain tissues, the evidence does not favour the existence of a universal threshold. The LNT hypothesis, combined with an uncertain DDREF for extrapolation from high doses, remains a prudent basis for radiation protection at low doses and low dose rates.*” (ICRP Pub 99, 2005). On this basis, “*The practical system of radiological protection recommended by the Commission will continue to be based upon the assumption that at doses below about 100 mSv a given increment in dose will produce a directly proportionate increment in the probability of incurring cancer or heritable effects attributable to radiation*” (ICRP Pub 103, 2007).

In recent years, a generally used terminology to indicate bands of radiation exposure is the one proposed by UNSCEAR in its 2012 Report (UNSCEAR, 2015). Low dose is defined as the range between 10 and 100 mGy, while moderate dose is defined as the range between about 100 mGy and about 1 Gy. These ranges are expressed as an approximate range of total absorbed doses of low-LET radiation (e.g., gamma radiation), additional to those from normal background exposure to natural sources of radiation. The range of low doses is interpreted as that in which an “*increased risk of cancer is plausible but not based on observed increased frequencies in populations that are deemed proven*” (UNSCEAR, 2015).

Today, even doses below several tens and a few hundreds of mGy are considered to require appropriate radiation protection measures (ICRP 2007). However, the opinion was also expressed that “*Due to large statistical uncertainties, epidemiological studies have not provided consistent estimates of radiation risk for effective doses less than 100 mSv*”. Furthermore, it was claimed that “*Considerable uncertainties remain for stochastic effects of radiation exposure between 100 mSv and 1,000 mSv …*” and that “*Epidemiological studies have not consistently demonstrated adverse health effects in persons exposed to small (less than 100 mSv) doses protracted over a period of many years*” (Health Physics Society 2020). This might imply that cumulated effective doses from recurrent imaging procedures (i.e., fractionated exposures) of the order of several tens or a few hundred mSv may not require specific attention, from the radiological protection point of view. Some authors proposed the idea of “*practical thresholds*” for carcinogenesis. “*This concept means that below the dose threshold, the carcinogenic risk, if it exists, is so small that it is without clinical importance.*” (Tubiana et al. 2009).

**Objectives**

To contribute to this discussion, the current paper summarizes the epidemiological evidence of radiation-related cancer, with particular emphasis on doses of low-LET ionizing radiation of several tens and a few hundred mGy (or mSv), and of higher cumulated doses if delivered at low dose rates or as a number of temporally separated low dose exposures. Health effects related to exposures to high-LET radiation are not considered in this paper. This article is not intended to be a systematic review, but rather a discussion of scientific reviews published about radiation-related cancer risks since the reviews of the US National Academy of Sciences (NAS 2006) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2008). The current paper considers studies of acute, repeated or chronic exposures. Low dose-rate is considered as being less than 0.1 mGy per minute, averaged over about one hour (i.e., <~5 mGy/h) (Unscear 2015)), but the intention is not to discuss in detail the effects of dose-rate, and detailed discussions of the influence of the dose-rates typical of the cohorts considered here can be found elsewhere (Rühm et al. 2018, Lowe et al. 2022).

As a first step, the article discusses studies on the Japanese atomic bomb survivors. In a second step, the paper summarizes recent findings from *pooled studies* and *meta-analyses* that include studies on radiation-exposed populations that do not individually show statistically significant radiation-induced risks. Finally, more recent studies on single populations exposed to ionising radiation, typically published since 2017, which were not included in the joint analyses mentioned above, are discussed.

**Recent Evidence of Radiation-related cancer risks - Japanese atomic bomb survivors**

In October 1950, a cohort of Japanese individuals who survived the atomic bomb explosions in August 1945 over Hiroshima and Nagasaki, Japan, was set up to study any radiation-related late effects among the survivors (Kamiya et al. 2015). This is the Life Span Study (LSS) cohort. The study was initially performed by the Atomic Bomb Casualty Commission (ABCC), and has been continued by the Radiation Effects Research Foundation (RERF) since 1975. Since 1950, 14 reports on mortality among the A-bomb survivors, and since 1958, three reports on cancer incidence, have been published.

**All Solid Cancers Combined**

Incidence

The third and most recent report on solid cancer incidence among atomic bomb survivors was published in 2017 (Grant et al. 2017). The study included 105,444 individuals (42,910 males, 62,534 females). During the follow-up period from 1958 to 2009, 22,538 first primary solid cancer cases (males: 10,473; females: 12,065) were observed. In their analyses, Grant et al. (2017) also included information on smoking (information available on about 60% of the studied individuals). For the studied survivors, individual organ/tissue dose estimates were available based on the most recent dosimetry system, DS02R1 (Cullings et al. 2017). In DS02R1, “weighted absorbed doses” are given in terms of absorbed dose from gamma radiation plus absorbed dose from neutrons multiplied by a factor of 10, to account for the increased biological effectiveness of neutrons as compared to gamma radiation. Because the studied individuals survived the explosions over Hiroshima and Nagasaki at various distances from the hypocenters (the hypocenter is the vertical projection of the point of explosion to the ground), their radiation doses cover a wide range from several mGy to several Gy. This fact allows the study of radiation-related effects (and in particular, radiation-related stochastic effects such as solid cancer and leukemia) over a wide dose range that includes doses between several ten and a few hundred mGy most relevant for the purposes of the present paper.

When a linear excess-relative-risk (ERR) model was applied to the solid cancer incidence data, the sex-averaged slope of the dose response (i.e., the ERR per weighted colon dose) was 0.47 Gy-1 (with a 95% confidence interval (CI): 0.39; 0.55 Gy-1). This result refers to an attained age of 70 years after exposure at age 30 years, adjusted for smoking. This result compares to an ERR coefficient of 0.47 (95% CI: 0.39, 0.55) Gy-1 reported by Preston et al. in the previous solid cancer incidence report (Preston et al. 2007), which demonstrates the overall consistency in risk estimates from the atomic bomb survivor cohorts. When individuals with high doses were gradually removed from the analysis the lowest dose range with a statistically significant dose response was for individuals with weighted colon doses of less than 100 mGy. In that case the sex-averaged ERR per weighted colon dose was 0.49 (95% CI: 0.026, 1.01) Gy-1 (Grant et al. 2017).

It is important to note, however, that the results are more difficult to interpret when sex-specific risk estimates are considered. In fact, Grant et al. (2017) report ERR values per weighted colon dose based on linear dose-response models of 0.33 (95% CI: 0.25; 0.42) Gy-1 and 0.60 (95% CI: 0.49; 0.72) Gy-1 for males and females, respectively (again, for an attained age of 70 years after exposure at age 30 years, and adjusted for smoking), which is a statistically significant difference between the sexes. For both males and females there was little evidence of a dose threshold, i.e., estimated threshold values were not significantly different from 0. These sex-specific ERR values per weighted colon dose are consistent with the results of the previous solid cancer incidence report where linear ERR/Gy values of 0.35 (95% CI: 0.27, 0.45) Gy-1 and 0.58 (95% CI: 0.40, 0.71) Gy-1 were reported for males and females, respectively (Preston et al. 2007), which again was a statistically significant difference. The reason for the obvious sex-specific difference is presently unclear. Moreover, while (Preston et al. 2007) found linear dose-responses for solid cancer incidence for both males and females, (Grant et al. 2017) found significant upward curvature in the dose-response for males so that a linear-quadratic dose-response model provided a significantly better fit than a linear model for males, but that a linear dose-response model was a satisfactory fit for females. Grant et al. (2017) concluded that “*At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies*”.

This aspect was examined in more detail by Cologne et al. (2019) who used the same data set as Grant et al. (2017). They applied two approaches, 1) excluding individual solid cancer sites or groups of sites from the analysis, and 2) applying a joint analysis with individual background-rate parameters used for various groups of cancers. Interestingly, when they applied a linear-quadratic dose response model to the data, they found that *the curvature decreased* significantly for males when five cancers (brain/CNS, esophagus, bone/connective tissue, thyroid, and non-melanoma skin) were excluded. In contrast, *the curvature increased* significantly for females when three cancer cites (breast, stomach, and thyroid) were excluded. Cologne et al. (2019) concluded that “*Analysis based on all solid cancer as a single outcome is not the optimal method …*” and that “*With nearly 60 years of follow-up there is now extensive information … so that heterogeneity across cancer sites … can now be accommodated.*”.

Consequently, and along these lines, a series of analyses has been performed by RERF recently on organ/tissue-specific radiation risks (see further below).

Mortality

Recently, Little et al. 2020 re-analysed the most recent LSS mortality data (Ozasa et al. 2012) in terms of solid cancer, leukaemia, and individual solid cancer sites (i.e., lung, stomach, breast cancer, all other solid cancers combined). In contrast to previous analyses of the data, they used updated dose estimates similar to those used by (Grant et al. 2017) and applied Bayesian techniques including adjustment for dose errors and model uncertainties to grouped data based on the mortality dataset published by Ozasa et al. 2012. They applied somewhat simpler ERR and EAR risk models involving linear-quadratic functions, and allowed for effect modifiers of sex, age at exposure, and time since exposure.

In terms of radiation-exposure induced deaths (REID) from solid cancers and for a UK population, Little and co-workers reported values of 3.57 Gy-1 (95% Bayesian credible interval (BCI): 0.70, 6.81), 3.88% Gy-1 (95% BCI: 1.17, 6.97), and 6.59% Gy-1 (95% BCI: 4.82, 8.46), for test doses of 0.01 Gy, 0.1 Gy, and 1 Gy, respectively. All results were given in terms of weighted colon absorbed dose, and analysis was restricted to doses of less than or equal to 3 Gy. The results obtained imply, in the relative risk model, a significant curvature for solid cancer versus weighted colon absorbed dose. No such curvature was found when lung cancer, stomach cancer and breast cancer were analysed separately. The curvature for solid cancer mortality remained when weighted colon absorbed dose was restricted to less than or equal to 2 Gy. The authors concluded that there was “*quite substantial dose-response curvature for most endpoints, in particular solid cancer …*” (Little et al. 2020).

**Site-Specific Solid Cancers**

Lung Cancer Incidence

Cahoon et al. (2017) used the data from the third solid cancer incidence report and investigated incidence specifically for lung cancer. They found 2,446 lung cancer cases in the investigated follow-up period (1958 – 2009). In their analyses they included smoking data such as smoking status (never, past, current, unknown), average number of cigarettes per day, age started smoking, years smoked, and years since quitting, and tested various models. For non-smokers, the ERR of lung cancer as a function of weighted absorbed lung dose, was described by a linear dose response, with the ERR/Gy = 0.81 (95% CI: 0.51, 1.18) for both sexes combined (at an attained age of 70 years following exposure at age 30 years), although the female-to-male ratio was a statistically significant 2.83. Inclusion of a quadratic term in dose response did not show any evidence of nonlinearity for males and females combined or separately (p>0.5). “*Furthermore, the sex-averaged dose-response relationship for a restricted range of 0–1.0 Gy (ERR/Gy = 0.65; 95% CI: 0.19, 1.21) is similar to that for the full range of 0–3.5 Gy (ERR/Gy = 0.81; 95% CI: 0.51, 1.18)*”. For smokers, the dose-response relationship was complex, with the ERR/Gy for low-to-moderate smokers being significantly higher than that for heavy smokers, the latter showing little evidence of any radiation-related excess risk of lung cancer, a finding that requires further investigation.

Breast Cancer Incidence

Brenner et al. (2018) used the data from the third solid cancer incidence report to investigate breast cancer incidence. They found 1,470 breast cancer cases for females and 10 for males. In their analysis of female breast cancer they included information on age at menarche, number of full-term pregnancies, age at first full-term pregnancy, and menopause status. For an age at exposure of 15 years and an age attained of 70 years, they did not find any significant departure from linearity when the ERR was analysed as a function of weighted absorbed breast dose. In fact, they reported that “*The linear ERR per Gy estimates were stable for successively lower dose ranges down to 0.250 Gy*”. They found a strong modifying effect of age at menarche, with higher ERR per breast dose for females with lower age at menarche, and for a given attained age and age at menarche, the breast cancer risk shows a maximum as age at exposure reaches menarche.

Colorectal Cancer Incidence

Sugiyama et al. (2020) used the data from the third incidence report and investigated colorectal cancer incidence. They found 2,960 colorectal cancer cases including 894 proximal colon (including ascending and transverse colon), 871 distal colon, and 1,046 rectal cancers. In their analyses they included information on smoking history, alcohol intake, meat consumption and body mass index. For total colon cancer, Sugiyama et al. (2020) found a significant dose response for colon cancers, linear with weighted absorbed colon dose, but little evidence of a radiation-related effect for rectal cancer. The authors did not perform any analysis of the dose-risk relationship on restricted dose ranges. Nevertheless, ERR values significantly higher than zero were found at 0.2 – 0.5 Gy and higher dose intervals (Sugiyama et al. 2019).

Cancer Incidence for liver, biliary tract and pancreas

Sadakane et al. (2019) used the data from the third incidence report and investigated incidence of liver, biliary tract and pancreas cancer. They found 2,016 liver cancers, 694 biliary tract cancers, 723 pancreatic cancers. Data on smoking history, alcohol intake, meat consumption and body mass index were included in their analyses. A significantly elevated ERR/Gy was found for liver cancer with no evidence for curvature in the dose response. Radiation dose was not associated with biliary tract cancer, but pancreatic cancer showed an increase in risk with dose that was statistically significant for women.

Cancer Incidence for uterus

Utada et al. (2018) used the data from the third incidence report and investigated incidence of uterus cancer. They found 224 uterine corpus cancers and 982 cervical cancers. Data on lifestyle and reproductive factors such as number of full-term pregnancies, age at first pregnancy, age at menopause, body mass index, and smoking history were included in their analyses. A significant ERR/Gy was found for uterine corpus cancer with no statistically significant departure from linearity in weighted uterus dose, while no radiation effect for cervical cancer was found. Specifically, a statistically significant increased risk was found for uterine corpus cancer, for the 11 – 15 years puberty group. This was, on average, 2-3 years earlier than the increased risk of breast cancer reported by Brenner and co-workers for young females (Brenner et al. 2018; Utada et al. 2018).

Cancer incidence for tumors of the central nervous system

Again, based on the most recent cancer incidence data among atomic bomb survivors (follow-up period (1958 – 2009)), Brenner et al. identified 287 tumors of the central nervous system (CNS) including non-benign and benign tumors such as gliomas, meningiomas, and schwannomas. For all CNS tumors combined, application of a linear dose response model gave an ERR/Gy of 1.40 (95% CI: 0.61, 2.57), and a test for quadratic departure from linearity was not significant. A statistically significant dose response was also found for glioma and meningioma, and each of the studied tumor types showed a dose response which was consistent with linearity. The authors emphasized, however, the “*substantial uncertainty in dose response*” (Brenner et al. 2020).

Prostate Cancer Incidence

Data from the third incidence report were also used by Mabuchi et al. to study prostate cancer among males of the Life Span Study cohort. The authors reported 851 prostate cancer cases among 41,544 male survivors. To estimate prostate dose, weighted absorbed dose to the urinary bladder was used. Lifestyle factors such as smoking, alcohol consumption and body mass index were not considered in the radiation risk analysis, because these factors did not significantly affect prostate cancer baseline rates among the study population. In contrast, temporal changes in baseline rates due to prostate-significant antigen (PSA) screening among the subset of males in the Adult Health Study were considered in the analyses. The authors found a statistically significant ERR/Gy of 0.57 (95% CI: 0.21, 1.00). They did not find any statistically significant deviation from linearity in a linear-quadratic dose response model, specifically that “*there was no indication of a statistically significant non-zero threshold effect in the dose response*” and reported a threshold estimate in a linear threshold model of 0.06 Gy (95%: 0, 0.67) (Mabuchi et al. 2021).

The above results for cancer incidence were largely confirmed in the study by Little and co-workers mentioned above (Little et al. 2020) who had re-analysed the LSS mortality data: while these authors found a significant curvature for all solid cancers combined for both males and females, they did not find any curvature for lung cancer, stomach cancer and breast cancer. In contrast, the identified curvature was entirely concentrated in the remainder category of all solid cancers excluding lung, stomach and breast cancer.

Table 1 summarizes the results of recent studies of solid cancer among atomic bomb survivors discussed in the present paper.

**Table 1**: Recent studies on solid cancer among atomic bomb survivors demonstrating significant radiation-induced health effects.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Endpoint** | **Follow-up** | **Number of investigated individuals** | **Dose infor-mation** | **Shape of dose response** | **Effect at low doses** | **Major conclusion** | **Reference** |
| All solid cancer incidence | 1958 - 2009 | 105,444 | several mGy – several Gy | Linear-quadratic shape for males;  Linear shape for females | Estimated dose threshold not different from 0 Gy;  For a linear excess-relative-risk model the sex-averaged slope of the dose response was 0.47 (95% CI: 0.39; 0.55) Gy-1, while that for the limited dose range of 0 – 100 mGy was still significant (i.e., 0.49 (95% CI: 0.026; 1.01) Gy-1) | *“At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies”* | Grant et al. 2017 |
| Solid cancer mortality | 1950 - 2003 | 86,611 | Colon dose ≤ 3 Gy | Significant curvature for solid cancers combined; no curvature for lung, stomach and breast cancer | - | “… *quite substantial dose-response curvature for most endpoints, in particular solid cancer …*” | Little et al. 2020 |
| Lung cancer incidence | 1958 - 2009 | 105,444 | Lung dose ≤ 3.5 Gy | No evidence for non-linearity (for never-smokers) | Sex-averaged dose-response for 0–1.0 Gy similar to that for 0–3.5 Gy | *“… the data from this study continue to provide the most detailed characterization of the joint effects of low-dose radiation and smoking on lung cancer risk”* | Cahoon et al. 2017 |
| Breast cancer incidence | 1958 - 2009 | 105,444 | Breast dose < several Gy | No significant departure from linearity | Linear ERR per Gy estimates stable down to 0.250 Gy | *“The study … continues to show a strong dose response for both female and male breast cancer.”* | Brenner et al. 2018 |
| Colorectal cancer incidence | 1958 - 2009 | 105,444 | Colon / bladder dose < several Gy | Significant linear dose response for total colon cancer;  quadratic term was not statistically signiﬁcant | Lowest dose group where an ERR value significantly higher than zero was found: 0.2 – 0.5 Gy | *“… the Life Span Study data continue to show a radiation effect on colon but not for rectal cancer.”* | Sugiyama et al. 2020 |
| liver, biliary tract, pancreas cancer incidence | 1958 - 2009 | 105,444 | Liver / pancreas dose < several Gy | Significant linear dose response for liver cancer | No evidence for curvature | *“… continued to provide evidence of a linear relationship … regardless of whether joint effects with smoking, alcohol consumption and BMI were considered.”* | Sadakane et al. 2019 |
| Uterus cancer incidence | 1958 - 2009 | 62,534 | Ovary dose < several Gy | no indication of a statistically significant departure from linearity for uterus corpus cancer | Lowest dose group where an ERR value significantly higher than zero was found: 1 – 2 Gy | *“… increased risk of uterine corpus cancer with radiation from atomic bombs among women exposed in mid-puberty with no apparent radiation effect for exposures before or*  *after this period.”* | Utada et al. 2019 |
| Cancer incidence in central nervous system | 1958 - 2009 | 105,444 | Brain dose < several Gy | Statistically significant linear dose response for glioma and meningioma; nearly significant linear dose response for schwannoma. | Test of quadratic departure from linearity was not significant | *“… while the linear model provides an adequate fit to the data, there is substantial uncertainty in dose response.”* | Brenner et al. 2020 |
| Prostate cancer incidence | 1958 - 2009 | 41,544 males | Urinary bladder dose < 4 Gy | Significant linear dose response | Threshold estimate in a linear threshold model: 0.06 Gy (95% CI: 0 to 0.67). | *“The observed dose response strengthens the evidence of a radiation effect on the risk of prostate cancer incidence in the atomic bomb survivors.”* | Mabuchi et al. 2021 |
| Leukaemia incidence | 1950 - 2001 | 113,011 | Bone marrow dose ≤ 4 Gy | Linear-quadratic dose response for leukaemias other than chronic lymphocytic leukaemia (CLL) and adult T-cell leukaemia (ATL), largely driven by acute myeloid leukaemia (AML);  Linear dose response for acute lymphoblastic leukaemia (ALL) and chronic myeloid leukaemia (CML). | - | *“The leukemia results indicated that there was a nonlinear dose response for leukemias other than chronic lymphocytic leukemia or adult T-cell leukemia … with much of the evidence for this nonlinearity arising from the acute myeloid leukemia risks.”* | Hsu et al. 2013 |
| Leukaemia mortality | 1950-2003 | 86,611 | Bone marrow dose ≤ 4 Gy | Substantial evidence for positive curvature in dose response | risk estimates (per unit dose) are approximately doubled when going from a test dose of 0.01 Gy to 1.0 Gy | *“This implies that the LDEF1 for cancer may be about 2 … although with substantial uncertainties”.* | Little et al. 2020 |

1 LDEF - low dose effectiveness factor

**Leukaemia**

Leukaemia, lymphoma and multiple myeloma incidence in the LSS cohort during 1950-2001 was studied by (Hsu et al. 2013). For leukaemias other than chronic lymphocytic leukaemia (CLL) and adult T-cell leukaemia (ATL), based on 312 eligible cases, a linear-quadratic dose-response model provided a significantly better fit to the data than a linear model. The estimated linear dose effect in the linear-quadratic ERR model at an attained age of 70 years following exposure at 30 years was 0.79 per Gy (95% CI: 0.03, 1.93), and the estimated curvature (the ratio of the quadratic to the linear dose coefficient) was 1.20 Gy-1. The ERR was found to depend jointly on log attained age and time-since-exposure, with the excess risk being greatest for those exposed at young ages and within a few years of exposure. There was evidence that the major types of leukaemia – acute myeloid leukaemia, chronic myeloid leukaemia and acute lymphoblastic leukaemia – although each displaying a significant radiation-related excess risk, may need to be considered separately in their response to radiation. Specifically, the observed upward curvature was largely driven by the 176 cases of acute myeloid leukaemia (AML), while the shape of the dose response curve was linear with no significant curvature for 43 cases of acute lymphoblastic leukaemia (ALL) and 75 cases of chronic myeloid leukaemia (CML).

In a re-analysis of the cancer mortality data from the atomic bomb survivors (Ozasa et al. 2012), Little and co-workers used updated dose estimates and applied Bayesian techniques including adjustment for dose errors and model uncertainties. Similar to solid cancers (see above), these authors found substantial evidence for upward curvature for leukaemia for which the risk significantly increased when the dose was increased from 0.1 Gy to 1 Gy (doses expressed in terms of weighted colon absorbed dose). For example, when doses in excess of 3 Gy were truncated, radiation-exposure induced deaths for a population in England and Wales increased from 0.35% Gy-1 (95% BCI: -0.03%, 0.78%) at 0.1 Gy to 1.14% Gy-1 (95% BCI: 0.75%, 1.56%) at 1 Gy (Little et al. 2020).

Studies on leukaemia are also included in Table 1.

**Recent Evidence of Radiation-Related Cancer Risks from Joint Analyses**

While there are studies on single populations that have enough power to provide statistically significant results on radiation-induced stochastic health effects, there are many studies on single populations exposed to ionizing radiation that do not (yet) demonstrate statistically significant radiation-induced stochastic health effects. This could be due to the fact that the cohort under study was too small to show any statistically significant effect, or that the effect to be detected was too small (e.g., because the involved radiation doses were too low). In such cases, a combined analysis of available studies could enhance the study outcome, either by pooling the raw data of several single studies and performing a joint analysis of the data, or by meta-analyses where a weighted average of the individual study outcomes is provided. Results of both approaches are summarized below.

**Pooled Studies**

Several pooled studies of the risks associated with low doses have been performed in recent years. The objective of such pooled studies is to analyse jointly data coming from different pre-existing cohorts. The advantages are the improve standardisation of inclusion criteria and homogenisation of methods, to allow testing for heterogeneity between cohorts, and increase statistical power. Table 2 summarizes the main characteristics of recent pooled analyses of cohorts.

*Solid cancer risk among nuclear workers*

The INWORKS project is a pooled study on nuclear workers, including 59,003 nuclear workers from France, 147,866 from the United Kingdom, and 101,428 for the United States. Periods of follow-up were 1968-2004, 1946-2001, and 1944-2005, respectively. For workers with cumulative dose greater than zero Gy, reported mean cumulative colon doses were 17.6 mGy, 22.5 mGy, and 20.0 mGy, respectively. Total number of workers was 308 297, and follow-up encompassed 8.2 million person-years. Of 66,632 known deaths by the end of follow-up, 17,957 were due to solid cancers. For the whole dose range (maximum colon dose: 1,332 mGy), application of a linear dose-response model provided – for all cancers other than leukaemia – a statistically significant ERR per Gy of 0.48 (95% CI: 0.15, 0.85)). The deduced radiation-induced risk remained statistically significant when the cumulated dose range was restricted to <200 mGy (1.04 (95% CI: 0.46, 1.66) Gy-1), and marginally so when restricted to <150 mGy (0.69 (95% CI: -0.01, 1.42) Gy-1). The authors concluded that their “*… study provides a direct estimate of the association between protracted low dose exposure to ionizing radiation and solid cancer mortality …*” (Richardson et al. 2015). The estimated risk per unit of radiation dose for cancer among radiation workers was similar to estimates derived from the Japanese atomic bomb survivors (Leuraud et al 2021). Analyses also showed a significant association between red bone marrow dose and non CLL-leukemia risk (ERR per Gy of 2.96 (95% CI: 0.83, 5.64)), still significant when dose range was restricted to 0-300 mGy (ERR per Gy of 3.31 (95% CI: 0.71, 6.52)) (Leuraud et al 2015) and marginally significant between lung dose and lung cancer risk (ERR per Gy of 0.56 (95% CI: -0.01 – 1.11)) (Richardson et al. 2018). The importance of INWORKS and other radiation worker studies is that doses have been accumulated as many small doses of radiation over protracted periods, often many years.

(Grellier et al. 2017) studied lung cancer mortality in a case-control study of workers from the UK, France and Belgium who were monitored for exposure to plutonium or uranium, a total of 553 deaths from lung cancer. The median external dose was 33 mGy and the maximum dose was 1,676 mGy. No dose-response was found for lung cancer mortality and external dose: the excess odds ratio (EOR) per Gy was -0.38 (95% CI: -0.62, 0.24) when adjusted for smoking and socioeconomic status.

(Gillies et al. 2017) studied lung cancer mortality and incidence in a joint study of Mayak and Sellafield workers, a cohort of 45,817 workers. Mean cumulative lung doses from external sources were 455 mGy for Mayak and 73 mGy for Sellafield, with maximum doses of 7,595 mGy and 1,848 mGy, respectively. The 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), using all available external doses. No deviation from a linear dose-response was detected and the ERR of was found to be significantly raised at doses of 300-400 mGy.

*Thyroid cancer risk after childhood exposure*

Lubin and co-workers performed a pooled analysis of thyroid cancer risk associated with low-dose radiation exposure (<200 mGy) in childhood (age at exposure <19 years). In the PIRATES study, nine cohorts were considered: eight medically exposed cohorts and the atomic bomb survivors. All cohorts together included 107,594 individuals, a mean follow-up period of 41 years, a mean thyroid dose of 30 mGy, and a total of 394 thyroid cancer cases (Lubin et al. 2017).

As a major outcome, a significant association between radiation dose and risk was observed even when thyroid doses were restricted to <100 mGy. There was no indication of any departure from linearity in the dose response, and estimates for any threshold dose were between 0.0 to 0.03 Gy (upper 95% CI: 0.04 Gy). Thus, the radiation-induced risk for thyroid cancer incidence persisted for more than 45 years after exposure, and was found to be greater at younger age at exposure and younger attained age, and similar by sex. The authors conclude that their “*analyses reaffirmed linearity of the dose response as the most plausible relationship for “as low as reasonably achievable” assessments for pediatric low-dose radiation-associated thyroid cancer risk.*” (Lubin et al. 2017).

*Leukemia risk after childhood exposure*

Little et al. performed a pooled analysis of leukemia risk associated with low-dose radiation exposure (<100 mSv) in childhood (age at exposure <21 years) (Little et al. 2018). The study included nine cohorts: eight medically exposed cohorts and the atomic bomb survivors. Altogether, the study included 262,573 individuals, a mean follow-up period of 20 y, and a mean cumulative dose to the red bone marrow of 20 mSv. Taking all studies together, 221 leukaemias were observed, excluding chronic lymphocytic leukaemia (CLL): 79 cases of acute myeloid leukaemia (AML), eight myelodysplastic syndromes (MDSs), 36 chronic myeloid leukaemia (CML), and 40 acute lymphoblastic leukaemia (ALL). In the study, a significant linear dose responses were found for AML, with a relative risk at 100 mSv of 2.56 (95% CI: 1.09–5.06), and ALL, with a relative risk at 100 mSv of 5.66 (95% CI: 1.35, 19.71); for ALL, a significant dose response was found below 20 mSv with a relative risk per 100 mSv of 45.09 (95% CI: 7.86–192.50). In general, there were only few indications of between-cohort heterogeneity and departure from linearity. The authors conclude that their “*findings support an increased risk of leukaemia associated with low-dose exposure to radiation and imply that the current system of radiological protection is prudent and not overly protective*” (Little et al. 2018).

*Risks of leukemia and thyroid cancer among Chernobyl liquidators*

Two nested case-control studies coordinated by IARC allowed the analysis of specific cancer risks with improved dose reconstruction among Chernobyl liquidators, pooling data from Belarus, Russia and the Baltic countries. The first analysis considered the risk of lympho-haematopoietic malignancies, including 40 leukemia cases, 20 Non-Hodgkin Lymphoma (NHL) and 10 cases other malignancies. . Most subjects received very low doses (median red bone marrow dose of 13 mGy). The estimated ERR/Gy for leukaemia excluding chronic lymphocytic leukemia (CLL) was 5.0 (95% CI: -5.5, 67) (Kesminiene et al. 2008). However, the ERR/Gy for CLL was 4.7 (95% CI: <0, 90), and for NHL was 28.1 (95% CI: -4.3, 284), which makes the findings difficult to interpret. The second analysis considered thyroid cancer risk, including 107 cases. Median total (external and internal) thyroid dose was 69 mGy. A statistically significant dose-response relationship was found, with an estimated ERR/Gy of 3.8 (95% CI: 1.0, 10.9) (Kesminiene 2012). 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.

Table 2 summarizes the results of recent pooled analyses of cohorts exposed to ionising radiation.

**Table 2**: Summary of recent pooled-analyses of studies of low to moderate doses

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Endpoint** | **Studied Individuals** | **Criteria** | **Exposure situations** | **Number of studies / subgroups** | **Number of subjects** | **Number of cases** | **Effect at low doses** | **Major Conclusion** | **Ref** |
| Solid cancer  Mortality | Nuclear workers from France, the United Kingdom and the United States | Workers monitored for external exposure | Cumulated low-LET occupational exposures (low-dose rate) | 3 | 308,297 | 17 957 | Significant association between colon dose and solid cancer mortality risk, even when dose range was restricted to 0-100 mGy | “O*ur data now yield sufficient statistical information to permit relatively precise estimates of cancer mortality risk in a population for whom average cumulative doses are about 20 mGy*.” | Richardson et al. 2015 |
| Lung cancer mortality | Workers from UK, France and Belgium | Monitored for exposure to plutonium or uranium | Cumulative external dose (at a low dose-rate) | 3 | 553 cases, 1,333 controls | 553 deaths | No significant excess lung cancer risk associated with cumulative external dose. | *“No dose response relationship was found for external radiation doses.”* | Grellier et al. 2017 \* |
| Lung cancer  Mortality and incidence | Combined cohort of Mayak and Sellafield workers | Plutonium workers monitored for external exposure | Cumulative external dose (at a low dose-rate) | 2 | 45,817 | 1,195 deaths  893 cases | Significant associations between external dose to the lung and lung cancer mortality and incidence.  ERR significant at 300-400 mGy. | *“Sensitivity analyses indicated that neither the external nor plutonium dose response had a significant quadratic component.”* | Gillies et al. 2017 |
| Thyroid cancer | Individuals with exposure during childhood | External dose below 200 mGy received before age 19 | Medical treatment for cancer or benign disease + atomic bomb survivors (high dose rate) | 9 | 107,594 | 394 | Significant association between thyroid dose and thyroid cancer risk, even when dose range was restricted to 0-100 mGy | “*Our analyses reaffirmed linearity of the dose response as the most plausible relationship for “as low as reasonably achievable” assessments for pediatric low-dose radiation-associated thyroid cancer risk*” | Lubin et al 2017 |
| Leukemia | Individuals with exposure during childhood | External dose below 100 mGy received before age 21 | Medical treatment for cancer or benign disease + medical diagnostic + atomic bomb survivors (high dose rate) | 9 | 262,573 | 221 | Significant association between RBM dose and leukemia risk, even when dose range was restricted to 0-50 mGy | “*These findings support an increased risk of leukaemia associated with low-dose exposure to radiation and imply that the current system of radiological protection is prudent and not overly protective.*” | Little et al. 2018 |
| Lympho-haemato-poietic malignancies, | Chernobyl liquidators from Belarus, Russia and the Baltic countries | Recovery workers who had worked around the Chernobyl plant in 1986–87 | Protracted radiation exposure. Median RBM dose of 13 mGy | 3 | 70 cases and 287 matched controls | 40 leukemia, 20 NHL and 10 other | A signiﬁcant increase was seen in all hematological malignancies combined at doses of 200 mGy and above | “*This study adds to the body of evidence on the effects of low-dose-rate exposures to ionizing radiation*.” | Kesminiene et al. 2008 \* |
| Thyroid cancer | Chernobyl liquidators from Belarus, Russia and the Baltic countries | Recovery workers who had worked around the Chernobyl plant in 1986–87 | External radiation + inhalation or ingestion of iodine-131. Median thyroid dose of 69 mGy | 3 | 107 cases and 423 controls | 107 | Significantly increased risk observed at doses of 300 mGy or above | “*The finding of our study contribute to the better characterization of the risk of thyroid cancer after radiation exposure in adulthood.*” | Kesminiene et al. 2012 \* |

NHL: Non Hodgkin Lymphoma; RBM : red bone marrow

\* : all pooled analyses are on cohort studies except three case-control studies

**Recent syntheses and Meta-Analyses of low dose studies**

Whereas few syntheses of cancer risks at low doses were published in the past (De Vathaire et al. 2005; Jacob et al. 2009), several have been published in the last five years. A summary of these syntheses is presented in Table 3. In addition to these systematic review papers, another interesting article can be cited, which aims to summarise the state of knowledge on the effects of low doses, with particular reference to epidemiological data (McLean et al. 2017).

*Comparison of other epidemiological studies with the LSS on Atomic bomb survivors*

(Preston et al. 2017) compared ERR/Gy estimates obtained from the Mayak Worker Cohort and Techa River studies with those derived from the LSS cohort. For the Techa River cohort, ERR per Gy estimates were for solid cancer mortality, 0.6 (95% CI: 0.1, 1.3); solid cancer incidence, 0.8 (95% CI: 0.1, 1.5); leukaemia incidence (without CLL), 2.2 (95% CI: 0.8, 5.4). Of interest is the similarity of the ERR/Gy estimates obtained from the Techa River residents protractedly exposed to low dose-rates and the Japanese atomic bomb survivors acutely irradiated. For the Mayak Worker Cohort, ERR per Gy estimates were for solid cancer mortality except lung, liver and bone, 0.2 (95% CI: 0.1, 0.3); leukaemia (without CLL), 0.1 (95% CI: -0.2, 0.5). These ERR/Gy estimates obtained from the Mayak Worker Cohort being 3 to 8 times lower than those derived from the Japanese atomic bomb survivors (Preston et al. 2017).

Currently, a task group of the ICRP is reviewing the scientific evidence on radiation risk at low-dose and/or low-dose rate exposures and considers radiation effects on various levels of biological organization (molecules, cells, animal models, humans). As part of their work programme, the TG performed a meta-analysis of radiation-induced solid cancer risk observed in epidemiological studies on cohorts exposed to low dose-rate radiation fields (Shore et al. 2017). While some of the individuals in these cohorts have been exposed to relatively high total doses of several 100 mGy (often dominating the risk estimates obtained in these studies), and a few other studies included even mean cohort doses of a similar order of magnitude, these doses typically consisted of single low doses accumulated over many years. Thus, these studies are of relevance for the present paper. The analysis included 22 epidemiological studies, some of these are discussed in the present paper (Mayak workers, Chernobyl clean-up workers, nuclear workers in the US, France and UK, Techa River population), and in addition eleven single studies on nuclear workers from various countries and three studies with environmental exposures (China, India, Taiwan). While these additional studies did not show any statistically significant increase in radiation-related solid cancer ERR per dose on their own, they nevertheless provide valuable additional information on the overall magnitude of radiation-related cancer incidence and mortality. Overall, the meta-analysis included data from more than 900,000 individuals. For all included studies corresponding risks from the LSS on atomic bomb survivors were calculated, matched for sex ratio and age distribution of the respective cohort. Comparison of the matched risks from the LSS with those form the low dose-rate studies allowed estimation of the effect of high dose-rate vs. low dose-rate exposures on radiation-related cancer risk, in terms of the corresponding ERR per unit dose ratios. The influence of each single study on the overall meta-analysis outcome was investigated by excluding the results of the individual cohorts one-by-one from the overall analysis. This approach resulted in combined risk estimates similar to those deduced from the LSS (in a range between 1 and about 2), with the cohort of the Mayak work force dominating the overall outcome. To focus on the most common range of today’s exposures in occupational, environmental or medical diagnostic settings, the authors further performed a sensitivity analysis restricted to 16 mortality studies with mean doses <100 (therefore excluding the Mayak worker study). The estimated meta-analytic ERR was still statistically significant (ERR per Gy = 0.41; 95% CI 0.12, 0.71) and the metanalytic LDR/LSS risk ratio was then 1.06 (95% CI 0.30, 1.83), with no indication of risk heterogeneity (Shore et al. 2017). The authors concluded that their data provide “*an important complement to the LSS risk estimates used for radiation protection purposes*” (Shore et al. 2017). The overall conclusion is that analyses of cancer risk estimates from the LSS (as summarized above) are supported by a considerable number of additional radio-epidemiological studies, even if their individual risk estimates are not significant on their own.

Hoel 2018 came to a similar conclusion (Hoel 2018). By applying a similar approach, he investigated 12 epidemiological studies on nuclear workers with at least 100 cancer deaths and calculated matched risks from the LSS on atomic bomb survivors. The results of this analysis were again dominated by the Mayak worker cohort and the cohorts of workers included in the INWORKS study. Furthermore, epidemiological studies on environmentally exposed cohorts in India, China, Taiwan, and the Southern Urals were discussed, as well as data from the Chernobyl clean-up workers and from Chinese medical X-ray workers. The author found a combined risk estimate which was about a factor 2 smaller than that deduced from the LSS and concluded that this result *“should be accepted with considerable caution since it is driven solely by the Mayak study*.” (Hoel 2018).

*NCRP LNT Analysis*

Implications of recent epidemiologic studies for the linear-non-threshold model in the context of radiological protection were studied in a recent commentary of the US National Council on Radiation Protection and Measurements (NCRP 2018, Shore et al. 2018). The report includes a critical review of studies published less than 10 years ago, primarily on radiation-related total solid cancer. Altogether, 29 studies (occupational, medical, and environmental exposures) were included in the analyses. In an effort to rate the quality of those studies, a number of quality criteria were applied with respect to epidemiology (design, follow-up, outcome ascertainment, confounding, etc.), dosimetry (quality of input data, dose reconstruction, consideration of dose uncertainties, etc.), and modelling (appropriateness of analytic method, adjustment, non-linear alternatives, etc.). Application of those criteria resulted in a composite score of specific strengths and weaknesses of each individual study and allowed an evaluation of how supportive the individual risk coefficients and the shape of the deduced dose-response curve was with respect to the linear-no-threshold (LNT) model.

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. Specifically, some studies were not precise enough to statistically exclude models with a dose-response threshold or an upward curvature in dose response, and there were a few studies with evidence of no risk after low dose exposures. The NCRP committee concluded that “ … *the LNT model, perhaps with a DREF >1, is prudent and practical for radiation protection purposes”* (NCRP 2018, Shore et al. 2018).

*NCI Monograph*

Recently, the US National Cancer Institute published a monograph on epidemiological studies on low-dose ionizing radiation and cancer (Berrington de Gonzales et al. 2020). The analyses included a total of 22 studies published since the BEIR VII report in 2006, with individualized dose estimates and mean doses of less than 100 mSv. All studies should provide risk estimates and confidence intervals for the dose-response for cumulative radiation dose. The primary objective was to conduct a formal assessment of the potential impact of confounding and biases such as selection bias, sources of dose errors, study power, loss of follow-up and outcome uncertainty, and model misspecification (Schubauer-Berigan et al. 2020; Daniels et al. 220; Gilbert et al. 2020). The systematic analysis of potential biases showed that “*these new epidemiological studies are characterized by several limitations, but only a few positive studies were potentially biased away from the null. After exclusion of these studies, the majority of studies still reported positive risk estimates*” (Hauptmann et al. 2020).

The second objective of the monograph was to perform a meta-analysis of selected studies with mean dose less than 100 mGy (Hauptmann et al. 2020). The aim was to quantify the magnitude of the risk, to assess the consistency across studies for both all solid cancers and leukemia, and to test the impact of excluding studies potentially biased away from the null. For adulthood exposure, the estimated meta-ERR at 100 mGy was 0.029 (95% CI 0.011 to 0.047) for solid cancers and 0.16 (95% CI 0.07 to 0.25) for leukemia. For childhood exposure, the estimated meta-ERR at 100 mGy for leukemia was 2.84 (95% CI 0.37 to 5.32). The authors concluded that “*new epidemiological studies directly support excess cancer risks from low-dose ionizing radiation. Furthermore, the magnitude of the cancer risks from these low-dose radiation exposures was statistically compatible with the radiation dose-related cancer risks of the atomic bomb survivors*” (Hauptmann et al. 2020).

*Meta-analysis of childhood medical diagnostic studies*

The increasing use of CT scanning as a powerful diagnostic tool offers a good opportunity for epidemiological studies to investigate the effects of low doses, especially on paediatric patients. However, the large numbers of study subjects required to obtain enough statistical power presents difficulties in obtaining reliable data (e.g., doses received) and in confidently excluding confounding. A recent article reviewed the literature on cancer risks associated with medical diagnostic exposures to ionizing radiation in childhood and assessed this risk through a meta-analysis (Abalo et al. 2020). The review considered relevant epidemiological studies published from 2000 to 2019, including patients younger than 22 years of age exposed to medical imaging ionizing radiation. A total of 21 studies were analyzed, including mostly patients who undergone X-ray examinations or CT scans. Among these, only six CT scan studies provided estimates of ERR per Gy and were used as the basis of a meta-analysis of the risk of leukemia and brain tumors. Interestingly, this analysis included a recent large Dutch cohort not included in previous syntheses (Meulepas et al. 2019). This cohort study included nearly 170,000 individuals who had received a CT scan while less than 18 years of age in the Netherlands. The study found an ERR per Gy for brain tumors (cumulative average dose to the brain: 38.5 mGy) of 8.6 (95% CI: 2, 22), while the ERR per Gy was 0.4 (-1.2, 16) for leukaemia plus MDS (cumulative dose to bone marrow: 9.5 mGy) and 2.1 (95% CI: -1.2, 24) for leukaemia with MDS excluded (Meulepas et al. 2019). Overall, the meta-analysis included 11,398,728 and 11,393,070 subjects for leukemia and brain tumor risk analyses, respectively. Among them, 437 leukemia and 478 brain tumor cases were observed. Results showed a significant increased risk for leukemia (ERR=26.9 per Gy, 95% CI: 2.7–57.1) and for brain tumors (ERR=9.1 per Gy, 95% CI: 5.2–13.1). For leukemia, sensitivity analyses in which each study was excluded one at a time revealed no substantial alteration of the estimated meta-ERR, except when excluding the recent Dutch study (Meulepas et al. 2019), which accounted for a large weight of the meta-analysis, leading to a higher meta-ERR after exclusion of this study. The authors concluded that “*CT exposure in childhood appears to be associated with increased risk of cancer*” (Abalo et al. 2020).

*Risk of in-utero exposures*

In the mid-1950s, the first evidence that low doses of radiation might increase the subsequent risk of cancer was published when the initial findings of a British case-control study of childhood cancer mortality showed an association with a radiographic examination of the abdomen of the pregnant mother, both for childhood leukaemia and other childhood cancers combined (Stewart et al. 1956). This study came to be known as the Oxford Survey of Childhood Cancers (OSCC), and the initial findings suggested that an antenatal X-ray examination approximately doubled the risk of childhood cancer. The results were controversial, but were confirmed by an extension of the study (Stewart et al. 1958) and importantly by a case-cohort study in the north-eastern USA that was entirely based on medical records and addressed some of the criticisms made of the OSCC methodology (MacMahon, 1962). Many other studies of childhood cancer in relation to an antenatal X-ray examination have been conducted globally, and a number of authors have attempted to combine the results of these studies in meta-analyses (Bithell, 1989; Bithell, 1992; Doll and Wakeford 1997; Wakeford, 2008). Most ecently, Wakeford and Bithell (2021) have combined the results of all case-control studies excluding the OSCC for various types of childhood cancer in meta-analyses, and compared the findings with those of the OSCC. In general, the relative risk estimates were compatible: for leukaemia, the RR was 1.51 (95% CI: 1.35, 1.69) for the OSCC and 1.28 (95% CI: 1.16, 1.41) for all other studies combined, while for all other childhood cancers combined the RR was 1.46 (95% CI: 1.31, 1.62) and 1.31 (95% CI: 1.13, 1.53), respectively. Wakeford and Bithell (2021) noted that the tendency for the RR to be lower for the other studies compared to the OSCC could be due to lower fetal doses received in later studies. The only type of childhood cancer for which there was a consistent absence of an association in the OSCC and the combined other studies was for bone tumours (which are not typical cancers of childhood).

Estimates of reliable fetal doses that would enable ERR/Gy to be derived from the case-control studies are sparse and ERR/Gy estimates have only been made for the OSCC. Fetal doses over the period covered by the OSCC were in the range of around 5-25 mGy, decreasing with calendar year of birth (Doll and Wakeford 1997). Using the OSCC data, an ERR/Gy estimate of 51 (95% CI: 28, 76) has been obtained (Doll and Wakeford, 1997; Wakeford and Little, 2003), but an alternative estimate of 29 (95% CI: 17, 44) has also been derived from the OSCC (Bithell and Stiller, 1988) that excludes later births, the data for which are considered less reliable. The absence of any case of childhood leukaemia among the Japanese atomic bomb survivors exposed in utero has been the subject of much comment (e.g., Boice and Miller, 1999), although the very small number (~0.2) of cases expected from Japanese rates in the mid-20th century must be borne in mind, and the intriguing absence of stable chromosome translocations at moderate and high doses in these survivors could point to a particular sensitivity to inactivation of haematopoietic cells in utero above 100 mGy leading to an absence of a notable risk of leukaemia (Ohtaki et al., 2004) (a potential explanation mooted by (Mole, 1974) almost half a century ago).

The consistent association between an antenatal X-ray examination and the risk of childhood cancer found in case-control studies implies that doses of a few tens of mGy can cause cancer – at least, most forms of childhood cancer following exposure in utero. As with all medical diagnostic exposures, the possibility of confounding must be seriously considered, but extensive searches for confounding factors has failed to identify any that could account for the association.

**Table 3:** Results of recent syntheses and meta-analyses of cohorts exposed to ionising radiation.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Objective** | **Criteria** | **Exposure situations** | **Studies** | **Conclusion** | **Ref** |
| Solid cancer \* and leukaemia without CLL | Comparison of ERR per Gy estimates between the LSS, the Mayak worker cohort and the Extented Techa River coheort | Adjustment of LSS estimates on characteristics of the Mayak and Techa River cohorts | Low-LET Occupational exposures | 2 | “*The Mayak Worker Cohort and Techa River Cohort provides evidence of longterm effects of low-dose rate*” | Preston et al. 2017 |
| Solid cancer  Mortality + incidence | Meta-analysis of the ratio of the ERR per Gy to the matching LSS ERR risk estimate (LDR/LSS). | LDR studies with dose-response risk estimates | Low-LET Occupational exposures, Environmental exposures; low doses accumulated over many years | 22 | The LDR data provide direct evidence regarding risk from exposures at low dose rates as “*an important complement to the LSS risk estimates used for radiation protection purposes*”. | Shore et al. 2017 |
| Solid cancer  Mortality | id | id + studies with mean dose < 100 mGy | id | 16 | Estimated meta-analytic ERR per Gy when restricted to studies with mean dose < 100 mGy | Shore et al. 2017 |
| Solid cancers | Meta-analysis of the ratio of the ERR per Gy to the matching LSS ERR risk estimate (LDR/LSS). | LDR mortality studies with dose-response risk estimates and with at least 100 cancer deaths | Low LET  Nuclear workers; low to moderate doses accumulated over many years | 12 | The combined risk estimate was about a factor 2 smaller than that deduced from the LSS. It is concluded that this result *“should be accepted with considerable caution since it is driven solely by the Mayak study*.” | Hoel 2018 |
| Solid cancer + Specific organs Mortality + incidence | Critical evaluation based on quality criteria on epidemiology, dosimetry and analysis | recent (<10y) low dose studies or group of studies: | Low-LET  Life Span Study, Worker Studies, Environmental Exposure Studies, High Background Radiation Area Studies, Childhood Medical diagnosis Studies | 26 | Most large and high-quality low-dose studies show positive risk coefficients, suggesting there may be cancer effects at low doses. Furthermore, it was judged that “*the*  *available epidemiologic data were broadly supportive of the LNT* (linear-no-threshold) *model and*  *that at this time no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes.*” | NCRP commentary 27, 2018 |
| Solid cancer Mortality + incidence | Systematic analysis of potential biases of low dose studies, and meta-analysis | recent (<10y) low dose studies with mean dose < 100 mGy and with dose-response risk estimates, and exclusion of studies with potential bias away from the null | Low-LET, Adulthood exposure; Worker Studies, Environmental Exposure Studies | 13 | Estimated meta-analytic ERR per Gy when restricted to studies with mean dose < 100 mGy.  *“New epidemiological studies directly support excess cancer risks from low-dose ionizing radiation”* | Hauptmann et al. 2020 |
| Leukemia Mortality + incidence | id | id | Low-LET, Adulthood exposure; Worker Studies, Environmental Exposure Studies | 14 | Estimated meta-analytic ERR per Gy when restricted to studies with mean dose < 100 mGy. | Hauptmann et al. 2020 |
| Leukemia Mortality + incidence | id | id | Low-LET, Childhood exposure; Environmental Exposure Studies, Medical diagnosis Studies | 6 | Estimated meta-analytic ERR per Gy when restricted to studies with mean dose < 100 mGy. | Hauptmann et al. 2020 |
| Leukemia and brain tumour incidence | Meta-analysis of childhood CT scan cohorts | Studies published from 2000 to 2019, including patients younger than 22 years of age at the time of CT scan | Low-LET, Childhood exposure; Medical diagnosis Studies | 6 | *“CT exposure in childhood appears to be associated with increased risk of cancer”* | Abalo et al. 2020 |
| Childhood cancer | Meta-analyses of results of case-control studies of childhood cancer and an antenatal X-ray examination | Comparison of the results of the Oxford Survey of Childhood Cancers with those of all other studies combined. Odds ratios presented for associations between the risk of childhood cancer and a preceding antenatal X-ray examination. | In-utero exposure to medical diagnostic radiation;  Typical fetal doses of 5-25 mGy X-rays, depending on calendar period of exposure. | 68 | *“Overall, the findings of this review strengthen the evidence for an increased risk of most types of childhood cancer consequent to the receipt in utero of a low dose of radiation, although a greater understanding of biological mechanisms is required for definitive conclusions to be drawn for specific types of cancer.”* | Wakeford and Bithell 2021 |

\* Solid cancer except lung, liver and bone cancers for the comparison with the Mayak worker cohort

CLL: Chronic Lymphocytic Leukemia

**Recent Evidence of Radiation-Related Cancer from Studies not Included in Combined Studies**

While the combined studies discussed above (pooled studies or meta-analyses) provide a rather clear and consistent picture (given the uncertainties involved in these studies), results of a number of single epidemiological studies that were not available at the time when the above-mentioned combined studies were published have recently been reported. These studies, which typically include data from longer follow-up or involve additional endpoints, are discussed below.

**Occupationally Exposed Cohorts**

*Nuclear worker studies*

A cohort of 167,003 UK nuclear workers (mean cumulative external dose: 25.3 mSv based on records of individuals’ dosimeters) was analysed in terms of cancer mortality and incidence and external dose for a follow-up period of 1955 - 2011 (Haylock et al. 2018). The authors of that study found a radiation-related solid cancer mortality ERR/Sv of 0.24 (95% CI: -0.03, 0.53) Sv-1 (footnote: while Haylock et al. provide 90% CIs, these have been converted to 95% CIs in the present work, to facilitate comparison with other study results), and a solid cancer incidence ERR/Sv of 0.22 (95% CI: 0.00, 0.46) Sv-1. When the dose range was restricted to < 400 mSv, <200 mSv and <100 mSv, the ERR/Sv estimates for cancer mortality increased and at < 100 mSv the ERR/Sv was 1.42 (95% CI: 0.34, 2.56) Sv-1. The authors concluded that their study “*provides direct evidence of cancer risk from low dose and dose rate occupational external radiation exposures*” and that “*Overall results are consistent with the risk estimates from the LSS and those adopted in the current ICRP recommendations*”.

Boice et al. (2021a) studied cancer mortality among 26,328 workers first employed at the Los Alamos National Laboratory between 1943 and 1980. Considerable efforts were made to reconstruct individual organ doses from external exposure to photons and neutrons, and from internal exposure due to incorporation of tritium and plutonium isotopes (238Pu and 239Pu). Radiation weighting factors for neutrons and alpha particles, and biokinetic models for plutonium were based on ICRP recommendations. The authors reported a statistically significant dose response for oesophageal cancer (ERR at 100 mGy: 0.29 (95% CI: 0.02; 0.55); mean weighted oesophagus dose: 12.9 weighted-mGy), and among those workers monitored for plutonium the standardized mortality ratio for bone cancer was increased (2.44 (95%CI: 0.98; 5.03); mean weighted dose to the bone: 26.4 weighted-mGy). In these cases, photons contributed more than 80% to total dose expressed in weighted-mGy. Other health endpoints including lung cancer and leukaemia did not show a statistically significant increase in radiation risk.

Boice et al. (2021b, accepted) studied mortality from leukaemia and cancer among 135,193 US nuclear power plant workers including a follow-up period from 1957 until 2011. Mean personal dose equivalent for the cohort was 49 mSv corresponding, for example, to a red bone marrow dose of 37.9 mGy (maximum 1.0 Gy; percent >100 mGy: 9.2%) and a colon dose of 43.7 mGy (maximum 1.1 Gy; percent > 100 mGy: 11.5%). Doses were mainly from external gamma radiation while doses from neutrons and from incorporation of radionuclides were negligible. There was marginal evidence for an increase in risk of leukaemia other than chronic lymphocytic leukaemia (CLL) (ERR per 100 mGy (95% CI): 0.15 (-0.03; 0.34)), and a linear and a linear-quadratic fit through the data performed equally well. The authors concluded that “*Prolonged exposure to radiation increased the risk of leukemia other than CLL* *among NPP workers.”* but that there was “*little evidence for a radiation-association for all solid cancers*”.

*Chernobyl Liquidators*

Ivanov et al. (2020) studied solid cancer incidence and mortality among 69,440 Russian male workers who were engaged in clean-up procedures in the Chernobyl exclusion zone in 1986-1987. The mean external dose was 133 mGy. In the follow-up period 1992–2017 a total of 6,981 incident solid cancers and 4,272 solid cancer deaths were reported. 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 [Note: actual CIs are not given and these CI estimates are derived from the plots presented in the paper.]. The minimum dose ranges over which a significant ERR/Gy was found were 0-175 mGy for solid cancer incidence and 0-200 mGy for solid cancer mortality. Ivanov et al. (2020) suggest that these minimum doses are compatible with those found after similar lengths of follow-up (i.e., 30-35 years) after exposure in the Japanese atomic bomb survivors (Cologne et al. 2018) and that the minimum doses will reduce with increasing length of follow-up of the Russian Chernobyl liquidators.

A cohort of 6,707 male cleanup workers from Lithuania was investigated by Smailyte et al. (2021). For cancer incidence, follow-up continued after their return from Chernobyl until end of 2012. Mean and median external doses were 109.6 and 99 mSv, respectively. Although the cohort was rather small and a significant increase in standardised incidence ratio (SIR) could not be identified when all cancers were combined, for thyroid cancers a statistically significant SIR of 3.13 (95% CI: 1.3, 7.52) was observed among young workers (age at entry into the zone: less than 30 years) with “official” doses greater than 100 mSv, although the possibility of surveillance bias must be considered. The authors conclude that this finding “*does not exclude causal relationship with radiation from Chernobyl*”.

*Veterans of nuclear bomb tests*

From 1945 through 1962, military personnel were exposed during the US atmospheric nuclear weapons tests, predominantly due to external radiation from radioactive fallout. A study on 114,270 male participants with reliable dose estimates suggested rather low radiation doses. For example, mean absorbed lung dose was 6.2 mGy with a maximum of 972 mGy, while mean absorbed dose to red bone marrow was 6 mGy with a maximum of 108 mGy. The study did not show any statistically significant radiation-related increase in cancer and leukaemia risk but “*excluded mortality risks per unit dose that are two to four times higher than those reported in other investigations*” (Boice et al. 2020).

*Medical radiation workers*

Another important radio-epidemiological cohort is the group of medical radiation workers in the United States. This cohort was recently studied for mortality due to lung cancer and leukaemia (Boice et al. 2021c, accepted). 109,019 individuals who were first monitored during 1965-1994 were included and their health status determined through 2016. Doses were estimated based on dosimeter readings adjusted for shielding and photon energy. However, dosimetry in this setting pose specific problems. Mean and median cumulated personal dose equivalents were 63 mSv and 37 mSv, respectively, with maximum values exceeding 500 mSv. This corresponded to mean cumulative absorbed lung dose of 13.0 mGy (maximum 1.27 Gy; percent >100 mGy 1.21%), while mean cumulative absorbed dose to RBM was 12.9 mGy (maximum 1.19 Gy; percent >100 mGy 1.01%). A significant ERR per 100 mGy for lung cancer was estimated as 0.15 (95% CI: 0.02, 0.27) while, for example, those for leukaemia other than CLL, breast cancer and brain cancer were not significant.

**Environmentally Exposed Cohorts**

*Exposures to Natural Background Radiation*

The evidence for an association between the risk of childhood cancer and exposure to natural background gamma radiation, including the results of geographical studies as well as those of individual-based studies, has been reviewed by (Mazzei-Abba et al. 2020; Milder et al. 2021). They concluded that it is hard to draw firm conclusions from the currently available findings, noting in particular the difficulties in obtaining accurate estimates of individual cumulative doses.

Very recently, two large ecological studies considered the potential risks of childhood cancers associated to background radiation in France. The first study investigated the association between natural background radiation exposure and childhood CNS (central nervous system) tumor incidence in France. The study included 5,471 cases registered over the period 2000-2012. Overall, no association between natural background radiation exposure and childhood CNS tumor incidence was observed, but an association was suggested between pilocytic astrocytomas and gamma radiation (Berlivet et al. 2020). The second study considered the risk of childhood acute leukemia (Berlivet et al. 2021). A previous study had considered the association between childhood acute leukemia incidence and natural background radiation exposure at the time of diagnosis (Demoury et al. 2017). Using the same methodology, the new study considered exposure at the time of birth (and therefore similar to the British study). The study included more than 6,000 childhood acute leukemia cases born and diagnosed in mainland France between 1990 and 2009. Similar to the previous study, no evidence was observed for an association between natural background radiation exposure and childhood acute leukemia incidence (Berlivet et al. 2021).

Jayalekshmy et al. (2021) investigated cancer incidence excluding leukaemia among the population of the high background radiation area of Kerala, India, based on a mean follow-up period of 19.1 years and including 6,804 cases. Individual doses from terrestrial radiation exposure were estimated for the cohort of 149,585 residents. Assuming a linear dose-response model, an ERR per colon dose of -0.05 (95% CI: - 0.33, 0.29) was obtained when adjusted for alcohol consumption, bidi smoking, tobacco chewing, and level of education. As compared to other radio-epidemiological studies this study gave a rather low ERR per Gy “*suggesting a possibility that the solid cancer risk associated with the continuous exposure to low-dose rate radiation is significantly lower than that associated with acute exposure*”. No quantitative results were provided for leukaemia, which is surprising given that 135 cases were available for study.

Mazzei-Abba et al. 2021 investigated the association of natural terrestrial gamma radiation, cosmic ray exposures, and exposures from 137Cs deposition from the Chernobyl accident with the incidence of childhood cancer in Switzerland. The study included almost 3.5 million children with age of less than 16 years for whom georeferenced residential locations were available. Incident cancer cases including relevant information on socioeconomic status and demographic factors were drawn from the national childhood cancer registry. They identified 3,137 incident cancer cases including 951 leukaemia cases, 495 lymphoma cases, and 701 cases of tumors of the central nervous system (CNS). For the whole cohort, median cumulative dose since birth was 8.2 mSv (range: 0 – 31.2 mSv). In terms of hazard ratios (HRs) the authors found values of 1.04 (95% CI: 1.01, 1.06) per mSv cumulative dose for all childhood cancers, 1.03 (95% CI: 0.98, 1.08) for leukaemia, and 1.06 (95% CI: 1.01, 1.11). The authors conclude that “*these results provide further support that external natural background radiation may contribute to observed cancer rates in children, particularly of leukemia and CNS tumors*”.

*Exposure to iodine-131 following the Chernobyl accident*

Two thyroid screening prevalence cohorts of persons aged under 18 years at the time of the Chernobyl accident, who had direct thyroid 131I activity measurement and were resident in the most radioactively contaminated regions, have been implemented respectively in Belarus and Ukraine. In 2017, an updated analysis of the Ukrainian-American cohort has been published, with follow-up extended to 2015. The cohort includes 10,073 individuals, with mean thyroid dose of 0.62 Gy (maximum dose of 41 Gy). Over the screening period 1998-2015, 80 cases were registered (47 thyroid cancers and 33 follicular adenomas). The ERR per gray estimates were 1.36 (95% CI: 0.39–4.15) and 2.03 (95% CI:0.55–6.69), respectively, for thyroid cancers and follicular adenomas. These new results including thyroid screening up to 2015 confirm that the excess risk of malignant and benign thyroid neoplasia persists nearly three decades after exposure (Tronko et al. 2017).

**Discussion**

**Scope of this synthesis**

This article is intended to contribute to the debate about radiation-related cancer risks in the low-dose range, based on studies published since the last reviews of the US NAS and UNSCEAR were performed (NAS 2006; UNSCEAR 2008). This article is not intended to be a systematic review of the literature and thus, the article does not claim to have identified all published results. Such a task would have been beyond the scope of the present paper, but is currently being undertaken by an UNSCEAR expert group with the aim to “provide a comprehensive scientific review of epidemiological studies of radiation and cancer to update annex A of the UNSCEAR 2006 report” (UNSCEAR 2021).

Emphasis was to include studies that report results at low or moderate doses. Therefore, some results deriving from analysis of cancer risk after radiotherapy, that are pertinent to assess cancer risk at higher dose levels, have been excluded (such as Allodji et al. 2021). Also, we considered only low-LET radiation exposure, so most of the studies considering internal contamination were excluded (with the exception of Iodine-131). In particular, results about cancer risks associated with alpha emitters (radon, uranium, plutonium) were considered out of the scope of this synthesis, but have been considered in detail in ICRP reports (ICRP 2010, ICRP 2021 plutonium).

In the first part of the article, recent studies reporting on evidence of radiation-related cancer and leukaemia risks among the Japanese atomic bomb survivors are discussed. This part is followed by the discussion of recent joint analyses of the results of radio-epidemiological studies, either pooled analyses or meta-analyses of relevant studies. Finally, a number of more recent additional studies (typically published since 2017) on single groups of radiation-exposed individuals are discussed that were not included in the joint analyses published so far (with no claim of completeness). This approach, somewhat unusual in a review paper, is related to the aim of the article, which is to answer to some claims that “*Epidemiological studies have not consistently demonstrated adverse health effects in persons exposed to small (less than 100 mSv) doses protracted over a period of many years*” (Health Physics Society 2020). Furthermore, this article should contribute to the discussions on whether or not effective doses of about 100 mSv due to recurrent CT scans require further attention.

**Relevance of Dose Rate**

The studies on atomic bomb survivors discussed above provide a good deal of evidence for significant radiation-related cancer risks at organ/tissue doses of about one or several hundred mGy. One might argue, however, that risk estimates deduced from studies on atomic bomb survivors may not be useful in estimating cancer risk of patients from recurrent CT imaging procedures, because there are differences in the exposure situations between both groups which might influence radiation-related risks in both groups.

The single exposure of the atomic bomb survivors was brief and involved different radiation sources – prompt primary gamma radiation, prompt neutron radiation, prompt secondary gamma radiation, delayed gamma radiation, and delayed neutron radiation. At a distance of 1000 m from the Hiroshima hypocenter, for example, major sources of weighted radiation dose (free-in-air kerma) were prompt neutrons (2.4 Gy), prompt secondary gamma radiation (1.4 Gy), and delayed gamma radiation (2.8 Gy). Because the duration of exposures was 10 μs, 0.2 s, and 10 s, respectively, the corresponding dose rates were 2.4⋅105 Gy/s, 6.9 Gy/s, and 0.28 Gy/s. Doses and thus dose rates decrease with increasing distance from the hypocenter (Rühm et al. 2018). However, in any event, dose rates were significantly higher than those typically encountered by patients receiving multiple repeated CT exposures (Lowe et al. 2022).

It has been argued that for low-LET gamma radiation, low-dose-rate exposure might be less harmful than high-dose-rate exposure, due to cellular repair processes, which are able to repair radiation damage such as DNA double strand breaks within a few hours of exposure. While such dose-rate effects have been observed in sub-cellular and cellular systems, and indeed, to some extent also among animal models, the situation is less clear for human carcinogenesis where the whole organism is affected and where the health outcome of interest – e.g., leukaemia and solid cancer – does not occur within a few hours but several years or even decades after exposure. In fact, a recent systematic comparison of radiation-related cancer risks for members of cohorts exposed at low-dose-rates (occupational, medical, environmental) with those from the atomic bomb survivors suggested risks from low-dose-rate exposures to be similar or 2 – 3 times less than those due to atomic bomb radiation (Shore et al. 2017; Hoel 2018).

**Relevance of Photon Energy**

The energy range of gamma radiation from the atomic bomb explosions over Hiroshima and Nagasaki was between 2 and 5 MeV, with a mean of about 3 MeV (Young and Kerr 2005, Cullings et al. 2017). In contrast, typical X-ray energies in medical imaging procedures are of the order of several tens of keV. A recent report published by the US National Council on Radiation Protection and Measurements (NCRP) evaluated the biological effectiveness of low-energy photons in inducing cancer in humans (NCRP 2017). They found, for example, that the 50% quantile of an estimated RBE frequency distribution in the energy range 40 – 60 keV is at an RBE value of about 1.4, when compared to 60Co gamma radiation. Thus, 40 – 60 keV X-rays may be 1.4 times more effective in causing cancer among humans than 60Co gamma radiation. For comparing the biological effectiveness of atomic bomb gamma radiation with that of 60Co gamma radiation, and in the absence of more relevant data, one might use data reported by Straume on the induction of dicentric chromosome aberrations in peripheral lymphocytes in blood from atomic bomb survivors. Their data suggest that 60Co gamma radiation might be a factor of 1.5 less effective in inducing dicentric chromosome aberrations than atomic bomb gamma radiation (but note as a caveat, that dicentric chromosome aberrations are not considered relevant for human carcinogenesis) (Straume 1995). Taken together, this might suggest that X-rays are a factor of about 2-3 more effective in inducing certain biological effects than atomic-bomb gamma radiation.

Taking both effects together one might argue that the lower dose rate and the higher biological effectiveness of X-rays as compared to atomic bomb gamma radiation at least partly compensate each other.

**Differences of criteria between recent syntheses or meta-analyses**

The interpretation of recent syntheses or meta-analyses published in the last five years (Table 3) should be performed carefully. Indeed, all these analyses provided information on cancer risks at low doses, but their objectives and criteria for selection of studies or definition of outcomes were not the same. For instance, the objective of the ICRP synthesis (Shore et al. 2017) was to investigate the impact of dose-rate, so only low dose-rate studies were included. The objective of the NCI monograph (Berrington de Gonzales et al. 2020) was to investigate results at low doses, so only studies with mean dose lower than 100 mSv were included. Nevertheless, we can underline that, when criteria are similar, then the obtained results are very coherent (see the sensitivity analysis of studies with mean dose below 100 mSv in (Shore et al. 2017) and the analysis of adulthood exposures in (Hauptman et al. 2020) in Table 3). These analyses show the impact of the inclusion or not of the Mayak worker cohort or of the Kerala background radiation study on the results.

**Uncertainties and biases at low doses**

Estimates of health risks from exposure to ionizing radiation are generally considered to be associated with large uncertainties, especially in the low dose range. These uncertainties are not only purely statistical uncertainties, but include other sources of uncertainty, e.g., those due to dose estimates, or choice of model for analysing epidemiological data (UNSCEAR, 2015). Also, it has been suggested that biases such as confounding and dose error could explain the positive findings of some recent epidemiological studies at low doses (Berrington et al. 2020).

UNSCEAR performed evaluations of selected health effects and inferences of risk from exposure to ionizing radiation (UNSCEAR 2020). In particular, the risks of leukaemia, all solid cancer and thyroid cancer were assessed in scenarios of exposure to ionizing radiation based on recent large epidemiological studies (repeated CT scans during childhood, occupational exposure in the nuclear industry, post-Chernobyl exposure during childhood). Results show that, for conditions that corresponded closely to those of the considered scenario, the best estimates derived from these studies were close to those obtained using effect-per-unit-dose estimates derived from the A-Bomb survivor cohort. A Monte Carlo approach of propagating uncertainties was applied to calculate credible intervals, thought to reflect both the statistical uncertainty and the potential impact of additional sources of uncertainty (selected populations, exposure assessment, health outcome assessment, study design, confounding factors, statistical methods and model uncertainties, other sources of uncertainty). Results showed that most additional stochastic sources of uncertainties relating to the exposure and follow-up conditions were small or very small (less than a factor 1.5), and rarely higher than a factor of 2 (only for age at exposure in the scenario of repeated childhood CT scans) (UNSCEAR 2020).

The US National Cancer Institute performed a systematic assessment of the potential impact of biases on recently published low-dose epidemiological studies (Berrington et al. 2020; Hauptmann et al. 2020). Analyses considered confounding and selection bias (Schubauer-Berigan et al. 2020), sources of dose errors (Daniels et al. 2020), loss of follow-up and outcome uncertainty (Linet et al. 2020), study power and model misspecification (Gilbert et al. 2020). The analysis of potential biases suggested that some recent epidemiological studies were characterized by several limitations, but only a few positive studies were potentially biased away from the null (such as for example the Chinese background study with possible bias away from the null because of a higher loss to follow-up in regions with lower background radiation exposure compared with regions with high background radiation exposure; the Canadian cardiac imaging study because those undergoing diagnostic or therapeutic procedures with imaging were more likely to have cancer outcomes detected, or the Korean radiation workers population where medical surveillance was required for radiation workers but not for the general population or for the worker comparison group). Furthermore, after exclusion of studies potentially biased away from the null, the majority still reported positive risk estimates. The authors concluded that the recent epidemiological results showing increased cancer risk at low doses were not likely to be due to methodological bias (Hauptmann et al. 2020).

It is noted that the NCRP Commentary (NCRP 2018) was not a systematic meta-analysis; instead it aimed to perform an evaluation of the quality of the studies, and to evaluate their support for the validity of a non-threshold risk model, but not to end up with a global meta-estimate. In this report, the selection process of considered studies was less formal, and in some cases, the quality assessment was applied to groups of studies and to individual studies.

Also, the different recent syntheses included results from *in utero*, childhood or adulthood exposures, and sometimes mixed results on all solid cancers and on specific cancer sites.

For all these different reasons, comparison of results between the different published syntheses must be performed carefully.

**Looking for a dose threshold**

Many studies tried to detect the minimal level of radiation exposure (Dmin), for which a statistically significant risk of radiation-induced cancer is observed (Tubiana 2009). Such an approach is methodologically limited as it is highly dependent on the statistical power and on the size of the studied population. When considering one specific cancer site instead of all cancers combined, the statistical power decreases, and therefore, the capacity to detect a Dmin at low dose is also reduced. The same occurs when males and females are considered separately instead of together. Furthermore, it has been recently demonstrated that such Dmin decreases with increasing duration of cohort observation, both in the cohort of Japanese A-Bomb survivors and in the cohort of Russian Chernobyl liquidators (Cologne et al. 2018; Ivanov et al. 2020).

A recent analysis of solid cancer incidence in the Life Span Study of atomic bomb survivors found evidence of differences in the curvature of the radiation dose response between males and females (Grant et al. 2017). Further analyses showed that heterogeneity of background rates between different groups of cancers might explain at least part of the all solid cancer dose-response difference in curvature between males and females, and that this heterogeneity was not captured by a background-rate model fitted to all solid cancers combined (Cologne et al. 2019). The authors concluded that analysis based on all solid cancers as a single outcome is not the optimal method to assess radiation risk for solid cancer in the Life Span Study (Cologne et al. 2019). It is probable that the orientation of future analyses will be to consider specific groups of cancer types instead of all solid cancers together, and to consider separately males and females. Such evolution will decrease the capacity to detect an excess risk at low dose levels, and therefore suggest that determination of a Dmin is not a proper approach.

The present synthesis shows that no dose threshold can be realistically proposed from the available epidemiological literature, for any of the reported health endpoints. Most studies that tried to estimate a threshold parameter found values compatible with an absence of threshold (Grant et al. 2017; Lubin et al 2017).

This is coherent with a recent review on biological mechanisms relevant for the inference of risk of cancer from low dose and low dose rate radiation conducted by UNSCEAR (UNSCEAR 2021). This report intended to synthesize the current knowledge on biological mechanisms of radiation actions at doses mostly in the low to moderate range relevant for cancer risk inference. Based on their review, the authors concluded that « *There remains good justification for the use of a non-threshold model for risk inference for radiation protection purposes, given the present robust knowledge on the role of mutation and chromosomal aberrations in carcinogenesis.* » (UNSCEAR 2021)

**Ongoing studies at low and moderate doses**

*Nuclear worker studies*

Occupationally exposed cohorts involve radiation doses and dose rates that are close to those typical for the radiation protection setting. Thus, the radiation cancer risks deduced from occupationally exposed cohorts might in the present context be considered more relevant than those deduced from the atomic bomb survivor cohort. There are a number of recent studies on nuclear workers that provide statistically significant radiation-induced cancer risks at doses relevant for the present paper.

Because the INWORKS pooled study on nuclear workers mentioned above (Richardson et al. 2015) included more than 300,000 individual workers, it could provide at least a borderline significant radiation-related cancer risk for cumulated doses of less than 100 mGy. An extension of the follow-up of this study is ongoing and should provide additional results on low dose cancer risks in the near future.

Another large-scale project is the Million Person Study (MPS) currently under way in the US, which might allow for quantification of radiation-related risk with an even larger database and, thus, perhaps find effects at even lower cumulative radiation doses (Boice et al. 2021c).

*Medical Exposures*

Although the focus of the present paper is not on radiotherapy studies, it is noted that in some cases such studies could also yield relevant results in the low- and medium dose regime (e.g., Little et al. 2018, Lubin et al. 2017).

Medical radiation exposures occur because a patient is either known to be (or to have been) ill or suspected of being ill or injured in some way. Irradiation of diseased cells is used as a therapy because the high doses delivered are capable of cell-killing. Inevitably, healthy cells close to heavily irradiated diseased cells also receive doses at some level, which can either lead to cell death or non-lethal cell modification that may be successfully repaired or eventually produce a malignant neoplasm. Studies of radiotherapy patients have demonstrated an increased risk of subsequent cancer, but the degree of increased risk is often modified by cell killing effects and possibly also by the nature of the disease being treated. The temporal distribution of the therapy must also be taken into account because fractionation of doses will lead to the repopulation of cells between sessions of therapy. A further consideration is the effect of other therapies, and the influence of concomitant chemotherapy is a particularly important consideration. For radiotherapy delivering localized high doses, doses received by organs/tissues away from the target volume of the therapy will receive a range of doses – organs/tissues close to the treatment site are likely to receive moderate to high doses either from being directly irradiated or from scattered radiation, while those organs/tissues remote from the target volume will receive lower doses from scattered radiation and distant organ/tissues may receive low doses. Doses from scattered radiation are difficult to calculate, but some sophisticated dose reconstructions have been carried out.

Studies of patients exposed for diagnostic purposes involve low doses, but pose their own problems in particular because of the possibility of reverse causation and confounding by indication. Reverse causation occurs when an investigation is undertaken because of the early effects of a small, slow-growing tumour that is only diagnosed later, while confounding by indication involves a medical condition that predisposes to cancer (e.g., Down syndrome to leukaemia) but also, in itself, requires a relatively high frequency of radiodiagnostic imaging. The reliable elimination of reverse causation and confounding by indication as explanations for an association between medical diagnostic exposure and subsequent cancer is a challenge to the accurate interpretation of results. Thus, results from studies on medically exposed individuals should be interpreted with care.

EPI-CT is a retrospective European multinational cohort of children and young adults subjected to CT at least once before the age of 22 years, and who have not been diagnosed with cancer either before or at the time of the first recorded CT nor within one year after it. The study aims to establish or expand existing cohorts in Belgium, Denmark, France, Germany, The Netherlands, Norway, Spain, Sweden, and the UK, and to include a total of more than 1 million children using an improved and standardized dosimetric approach. This project will allow for a large statistical power, and should also provide some insight in the potential impact of reverse causation and indication biases (Bernier et al . IJE 2019; Thierry-Chef et al., RR 2021).

*Environmental studies*

Studies of cancer and exposure to natural background gamma radiation are a useful addition to the evidence for low levels of radiation exposure increasing the subsequent risk of cancer, but the generally low doses involved require large studies to provide sufficient statistical power to produce meaningful results, which presents a challenge. The studies of cancer mortality in Yangjiang, China, (Tao et al. 2012) and cancer incidence in Kerala, India (Nair et al. 2009; Jayalekshmi et al. 2021) are of interest in that little evidence for an increase of cancer risk associated with background radiation exposure was found, but the limitations of these studies have been discussed by (UNSCEAR, 2018 #53)} and (NCRP, 2018). The Kerala study needs “*to increase efforts to improve their cancer ascertainment and diagnosis, and to closely examine the impact that low income/education and distance from the principal cancer facilities may have on cancer ascertainment rates. Further carefully designed validation studies of reconstructed doses by personal dosimetry measurements would also be valuable*” (NCRP 2018). Studies of childhood cancer and background radiation (Mazzei-Abba et al. 2020) are a potentially promising approach, but large studies are required, which pose a number of difficulties, and current results are mixed.

Cancer occurrence in residents of riverside communities affected by radioactive contamination of the Techa River by discharges from the Mayak nuclear complex in Russia during the late-1940s and 1950s has been studied with some evidence of an increased risk, but the problems posed by dose reconstruction and adequate tracing of individuals should not be underestimated (UNSCEAR, 2018; NCRP, 2018). Similar concerns apply to the relatively small Taiwanese cohort exposed to gamma radiation from Co-60 contaminated structural steel (Hsieh et al. 2017).

**Conclusions**

In contrast to other genotoxic substances, there is a vast body of literature available on the long-term effects of ionising radiation on the human body. Even before the atomic bomb explosions over Hiroshima and Nagasaki, studies had suggested that exposure to ionising radiation might be responsible for an increased rate of cancer. After 1945, various studies on the Japanese atomic bomb survivors consistently demonstrated an increase in cancer and leukaemia mortality above a dose of several 100 mGy. With increasing length of follow-up and statistical power, radiation doses for which a statistically significant radiation-related effect could be demonstrated continuously decreased and, consequently, it currently appears that there is increasing evidence for radiation-related increases in cancer and leukaemia rates around 100 mGy and even below 100 mGy. Based on the discussion above it is concluded that data from the LSS are relevant for radiation-related risks of patients receiving recurrent CT imaging procedures, and also for many other exposure situations (Unscear 2020).

Complementary to studies on the atomic bomb survivors an increasing number of studies on other populations have also been conducted. These populations include workers (e.g., nuclear workers, clean-up workers, medical workers), populations with environmental exposures (e.g., the population residing along the Techa River in the Russian Federation, populations living in high background radiation areas, populations with incorporation of radioiodine after the Chernobyl accident), and those exposed for medical reasons (due to medical imaging and radiotherapy). Although the typical radiation doses to these populations are often lower than those of the atomic bomb survivors, quite a number of these studies also provide evidence for a radiation-related excess of cancer and leukaemia rates, at several hundred mGy and approaching 100 mGy.

The dose levels that permit the detection of radiation-related excess cancer and leukaemia rates depend on the statistical power of studies, which, in turn, can be improved by increasing follow-up periods and/or increasing the number of studied individuals. Consequently, the dose levels that currently allow the quantification of radiation-related excess rates should not be interpreted as “magic” threshold levels, but rather represent a snapshot of the current state of knowledge on the induction of long-term health effects due to exposure to ionising radiation. 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. First indications on this have been given in the present article (see, e.g., discussion of the pooled studies of leukaemia and thyroid cancer, and of childhood cancer after in-utero exposures).

Along these lines, leading international cancer research institutions and consortia have performed joint analyses (pooled or meta-analyses) of relevant data and concluded recently that there is growing evidence on the carcinogenic effects of low-dose ionising radiation, and that a linear extrapolation to even lower doses for estimating radiation-related cancer risk is reasonable for radiological protection purposes. The US National Council on Radiation Protection and Measurements has recently concluded that *“… the LNT model … is prudent and practical for radiation protection purposes*” Furthermore it was judged that “*the available epidemiologic data were broadly supportive of the LNT (linear-no-threshold) model and that at this time no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes.*” (NCRP 2018, Shore et al. 2018). In a synthesis coordinated by the US National Cancer Institute, a meta-analytic ERR per Gy was estimated using studies with mean dose <100 mGy. It was concluded that “*New epidemiological studies directly support excess cancer risks from low-dose ionizing radiation*” (Hauptmann et al. 2020). After having compared risk estimates from 22 studies on low dose-rate exposures typically consisting of single low doses accumulated over many years with matched risk estimates from the atomic bomb survivors, Shore et al. (2017) obtained direct evidence regarding risk from exposures at low dose rates and concluded that this is “*an important complement to the LSS risk estimates used for radiation protection purposes*”. In a pooled study on nuclear workers from three countries (US, UK, France) Richardson et al. (2015) concluded that their “*data now yield sufficient statistical information to permit relatively precise estimates of cancer mortality risk in a population for whom average cumulative doses are about 20 mGy*.”. Lubin et al. (2017) studied thyroid cancer risk after childhood exposure in 9 study groups. They found that their analyses “*reaffirmed linearity of the dose response as the most plausible relationship for “as low as reasonably achievable” assessments for pediatric low-dose radiation-associated thyroid cancer risk*”. Among individuals exposed during childhood with whole-body doses of less than 100 mGy, Little et al. (2018) found support of an “*increased risk of leukaemia associated with low-dose exposure to radiation*” and concluded “*that the current system of radiological protection is prudent and not overly protective.*”. Finally, Wakeford and Bithell (2021) reviewed the available literature of childhood cancer risk after in-utero diagnostic exposure and concluded that “*the findings of this review strengthen the evidence for an increased risk of most types of childhood cancer consequent to the receipt in utero of a low dose of radiation, although a greater understanding of biological mechanisms is required for definitive conclusions to be drawn for specific types of cancer*.”.

A number of these studies suggest that cellular repair mechanisms that are active after exposure to ionizing radiation do not prevent radiation-related cancer occurring after low-level exposure of humans to ionising radiation. Consequently, the low doses received by patients exposed to recurrent CT imaging procedures cannot be ignored as there is a real potential for an increase in radiation-related cancer risk (Unscear 2021).

The fact that exposure to even low doses of ionising radiation might pose some increase, albeit small, in cancer and leukaemia risk, implies that a careful analysis of these risks against any benefit that may be gained from such exposure is indispensable. For almost a century the International Commission on Radiological Protection has been working on evidence-based guidance and recommendations to support individuals and societies in balancing the benefit and risk of radiation exposures under various conditions. These guidelines and recommendations draw upon more than 125 years of radiation research on the health effects of ionisation radiation, which began immediately after the discovery of x-rays in 1895.

With this in mind, we conclude that continuous research is needed to steadily deepen our understanding of the action of ionising radiation on sub-molecular, molecular, cellular, tissue, and organism levels. If any risks that might be present are properly understood then appropriate actions can be taken to keep associated negative effects as low as reasonably achievable, and attention can be focused on the beneficial consequences of ionising radiation exposure. To support this process, the ICRP has recently identified areas of research to support the system of radiological protection (Laurier et al. 2021; see also Clement et al. 2021).

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