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Review paper

Risk of low-dose radiation and the BEIR VII report: A critical review of what it does and doesn't say

Michael K. O'Connor

Mayo Clinic, Section of Nuclear Medicine, Charlton 1-225, Rochester, MN 55905, United States

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ABSTRACT

This article briefly reviews the history behind the BEIR VII report and the use of the linear no-threshold hypothesis. The BEIR VII committee considered four primary sources of data on the stochastic effects of ionizing radiation. These were environmental studies, occupational studies, medical studies and studies on the atomic bomb survivors. These sources are briefly reviewed along with key studies that run counter to the LNT hypothesis. We review many of the assumptions, hypotheses and subjective decisions used to generate risk estimates in the BEIR VII report. Position statement by the Health Physics Society, American Association of Physicists in Medicine, and UNSCEAR support the conclusion that the risk estimates in the BEIR VII report should not be used for estimating cancer risks from low doses of ionizing radiation.

Contents

1. Introduction

The topic of radiation associated risks is one that has come to prominence over the last 10 years with the significant increase in the use of ionizing radiation in medical imaging. This topic, coupled with well-publicized events such as the Fukushima nuclear accident has heightened public awareness of this issue. People fear what they do not understand and radiation risk is a textbook example of a topic that is poorly understood and feared by both patients and physicians [1]. In an Op-Ed article in the New York Times (Oct 21, 2013) entitled "Fear vs. radiation: the mismatch", David Ropiek discussed our fear of radiation which stems from our understandable fear of the power of nuclear weapons and went on to state that "*... in the 70 years since Hiroshima and Nagasaki, epidemiological and scientific studies have shown that at radiation doses of less than 100 mSv, radiation causes no detectable elevations*

E-mail address: mkoconnor@mayo.edu

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in normal rates of illness and disease. Yet our response to radiation continues to contradict the robust evidence that ionizing radiation is a relatively low health risk".

The increased exposure of patients to medical radiation has caused some authors to predict thousands of radiation-induced cancers in the US population in the coming years. One study predicted an annual toll of 14,500 cancer deaths from CT examinations [2], and Brenner and Hall [3] estimated that CT scans will be responsible for 1–2% of all future cancers in the U.S. These predictions and several others like them [4,5] stem from risk estimates derived from reports by the committee to assess health risks from exposure to low levels of ionizing radiation. This committee is under the auspices of the National Academy of Sciences. The most recent report [6] is known as the Biological effects of Ionizing Radiation (BEIR) VII Phase 2 and was issued in 2006. A National Academy of Sciences press report at the time [7] quoted the chair of the committee, Richard R. Monson, as stating "*The scientific research base shows that there is no threshold of exposure below which low levels of ionizing radiation can be demonstrated to be harmless or beneficial* ". The press report went on to state that "*Living at low altitudes, where there is less cosmic radiation, and living and working on the upper floors of buildings, where there is less radon gas — a primary source of natural ionizing radiation — are factors that could decrease exposure*". Given the prominence that this report has in our understanding of the risks associated with low doses of ionizing radiation, and the inherent warnings in the accompanying press release, it is important to be aware of the limitations in the data used to generate its risk models, and the assumptions inherent in these risk models.

2. Historical perspective

The BEIR VII report is the latest in a series of reports that span over 60 years, starting with the BEAR committee in the 1950 s. A key component of the risk models developed by the BEIR VII committee is the use of the linear no-threshold (LNT) hypothesis. This model was originally proposed in 1928 [8] to account for genetic changes in the genome from background ionizing radiation, thereby offering an explanation of Darwin's theory of evolution. While this theory was shown to be incorrect with respect to the mutagenic effects of radiation, the LNT model became adopted by the radiation genetics community in an attempt to predict the carcinogenic effects of ionizing radiation [9,10], and eventually was adopted by the first committee on the biological effects of atomic radiation (BEAR) [11]. In the late 1960s, this committee was renamed the BEIR (Biological Effects of Ionizing Radiation) committee.

Given the prestige of the National Academy of Sciences, the recommendation by the BEIR committee to use the LNT model has been widely adopted both in the US and elsewhere. This has occurred despite numerous scientific studies and review articles that highlight the inadequacy of the LNT hypothesis to explain the carcinogenic effects of low doses of ionizing radiation [12–16].

3. BEIR VII – sources of data on stochastic effects of ionizing radiation

The BEIR VII committee considered four primary sources of data on the stochastic effects of ionizing radiation. These were environmental studies, occupational studies, medical studies and studies on the atomic bomb survivors. Below we have briefly reviewed some of the key studies in each of these areas.

3.1. Environmental studies

The BEIR committee reviewed studies from 1990 through 2004 and concluded that most were ecologic in design and therefore of limited value in estimating the cancer risk from ionizing radiation. These included studies of populations living near nuclear facilities, populations exposed to atmospheric testing or other environmental release of radiation, populations exposed from Chernobyl and populations exposed to high natural background radiation. The studies of greatest interest are those relating to Chernobyl. While there was strong evidence of increase in thyroid cancer due to the high doses of I-131 released, the BEIR VII report concluded that "*there is no evidence of an increase in any solid cancer type to date*" (BEIR VII, page 228).

The committee reviewed 4 studies of populations living in areas of high natural background radiation in China and India. No increase in disease rate was observed in any of these studies. One study not included in their review was that of Tao et al. [17]. They performed a 26-year study of over 125,000 subjects living in an area of high natural background radiation in Yangjiang, China. Risk estimates were negative (i.e. radioprotective effect), although this did not reach statistical significance.

Because these studies were descriptive in nature and ecologic in design, they were considered of limited use by the BEIR VII committee, and largely dismissed from further consideration. This is unfortunate as the absence of an effect in so many studies is itself an indication that the effects of radiation may not follow the LNT model of radiation risk.

One topic not included in the review of environmental studies by the BEIR VII committee was radon exposure. This was reviewed in an earlier BEIR VI report [18] which had concluded that ~19,000 excessive lung cancer deaths occur annually in the U.S. due to residential radon exposure. This was based on data from miners who are exposed to radon levels orders of magnitude higher than those found in residential homes. A more recent prospective study of ~1.2 M participants showed positive associations between ecological indicators of residential radon and lung cancer [19]. Participants with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% (95% CI, 7–68) increase in risk for lung cancer mortality relative to those below the guideline value. The authors concluded that their study supported "*further efforts to reduce radon concentrations in homes to the lowest possible level*" [19]. In one of the most rigorous case-control studies of lung cancer incidence vs. residential radon exposure, Thompson et al. [20] found that the odds of lung cancer did increase for radon levels above the EPA guideline value, in agreement with the study of Turner [19]. However, at radon levels below the EPA guideline value, they found a statistically significant hormetic effect of radon on lung cancer (Fig. 1). This finding runs contrary to the recommendation from Turner et al., and from the National Academy of Sciences press release for the BEIR VII mentioned above.

3.2. Occupational radiation studies

Occupationally exposed workers in the nuclear power industry are in theory an ideal group in which to study the effects of low levels of ionizing radiation. The BEIR VII committee reported that "*in most of the nuclear industry workers studies, rates for all causes and all cancer mortality in the workers were substantially lower than the reference population*" (BEIR VII, page 194). The BEIR VII committee concluded that "*possible explanations include the healthy worker effect and unknown differences between the nuclear industry workers and the general population*" (BEIR VII, page 194). As a result, the BEIR VII committee eliminated them from further consideration. One of the most intriguing studies that was not reviewed by the BEIR VII committee was that of Sponsler and Cameron [21]. They

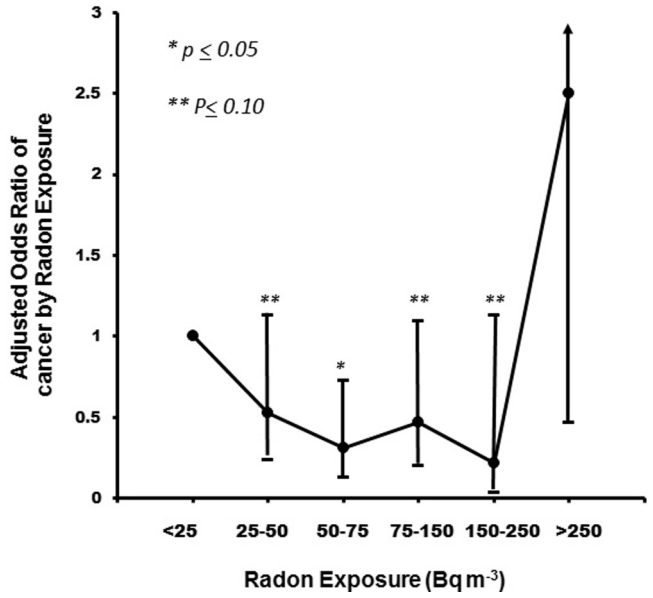

Fig. 1. The adjusted odds ratio (95% CI) of lung cancer as a function of radon concentration in the home. Results adjusted for smoking, residency, work exposure and education. Adapted from Table 3, Thompson et al. [20]. Note EPA guidelines recommend residential radon levels <148 Bq/m^3.

reviewed the results from the nuclear shipyard worker study (NSWS) [22]. The NSWS is unique in that it is one of the few radiation studies where age-matched and job-matched unexposed workers were used as controls. This was designed to avoid the 'healthy worker effect' that resulted in the elimination of other large scale studies of nuclear power workers. The NSWS used a large cohort of 27,872 nuclear workers and 32,510 job and age matched controls from non-nuclear shipyard workers. Fig. 2 shows the standardized mortality ratio as a function of annual dose. The high-dose workers demonstrated significantly lower all-cause mortality than did unexposed workers. The original report [22] concluded that "*the all-cause mortality is highest for the NNW (control) group and lowest for the NW > 0.5 (radiation > 5 mSv) which certainly does not suggest that radiation causes a general risk of death*". The findings of this study are incompatible with the LNT model of radiation risk.

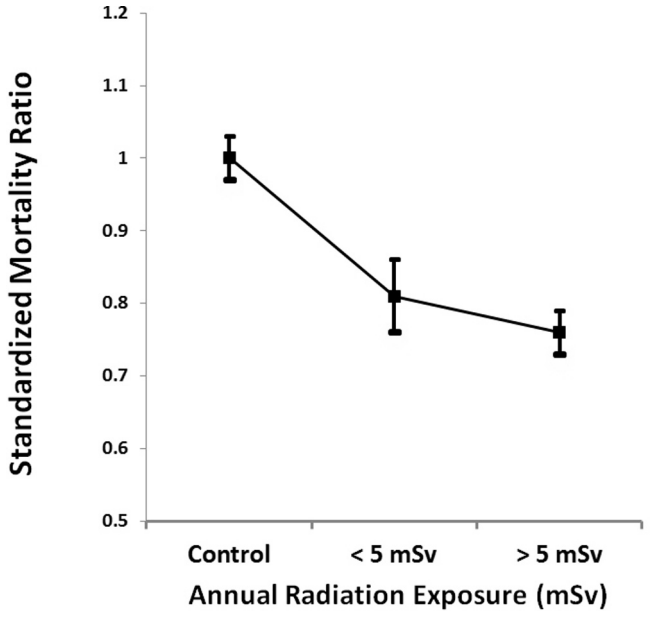

Fig. 2. Standardized mortality ratio as a function of annual radiation exposure in nuclear shipyard workers. Adapted from Table 1, Sponsler and Cameron [21].

3.3. Medical radiation studies

The BEIR VII report devotes a large section to the analysis of studies of radiation-treated patients that have been followed for long periods of time. Many of these studies contained large populations that rival those studies after the atomic bombings. The BEIR VII committee looked at publications on radiation risk for 5 types of malignancies (lung cancer, female breast cancer, thyroid cancer, leukemia and stomach cancer). The largest study was that of Howe who reported on the incidence of lung cancer after a 40-year follow-up period in a cohort of over 64,000 tuberculosis patients who received high doses of radiation from multiple fluoroscopies [23]. Because of the high radiation doses associated with many of these studies, the committee was able to derive risk estimates using a linear model to describe the relationship between dose and cancer incidence. For lung cancer, the risk estimates from medical studies (BEIR VII, Table 7–2) had a mean value of 0.38/Gy (excess relative risk per Gy) and a weighted mean value of 0.06/Gy. By comparison, the value obtained from the atomic bomb survivor studies (BEIR VII, Table 6–2) was 0.80/Gy, and the final value chosen by BEIR VII committee (BEIR VII, Table 12–2) was 0.86/Gy. As discussed below, the BEIR VII committee placed far great weight on the risk estimate from the atomic bomb survivor data, despite the fact that the medical populations are closer in ethnicity, lifestyle and diet to the US and European populations.

3.4. Atomic bomb survivor studies

Following the end of World War II, the. U.S. and Japanese governments set up the Radiation Effects Research Foundation (RERF) to study and document the aftereffects of the atomic bombings in Hiroshima and Nagasaki in 1945. A cohort of ~120,000 subjects has been included in this program and they have been extensively monitored since 1947. Analysis of the cancer incidence in this population forms the basis for almost all risk estimates by the BEIR VII committee. The BEIR VII report itself does not review or discuss the raw data from this cohort, but instead relies on published risk estimates from analysis of this cohort. This data is central to the deliberations of the BEIR VII committee, and hence it is important for the reader to be familiar with some key findings from these studies that are at variance with the LNT hypothesis.

The two most recent published studies report on the number of cancers after 40-years of follow-up (from 1958 to 1998) [24], and after 53 years of follow-up (from 1950 to 2003) [25]. Fig. 3 plots the number of solid cancers at each radiation dose level taken from Table 4 of Preston et al. [24], and from Table 9 of Ozasa et al. [25]. We have adjusted the data points to units of cancers/100,000 people. In both studies, the weighted dose to the colon served as a surrogate for effective whole body dose. There are several notable features to this figure. First the longer follow-up period of 13 years should have resulted in the accumulation of additional radiation-induced cancers, but instead we see fewer cancers per 100,000 across all radiation doses. The solid circle in Fig. 3 represents the results for inhabitants of Hiroshima and Nagasaki who were not in the cities at the time of the bombings and hence received none of the blast radiation. Cancers for this group were similar to those seen at doses of less than ~100 mGy. After 53 years of follow-up a significant increase in the number of cancers is only observed at higher doses. Preston et al. [24] stated that "*based on fitting a series of models with thresholds at the dose cut points. . .., the best estimate of a threshold was 0.04 Gy with an upper 90% confidence bound of*

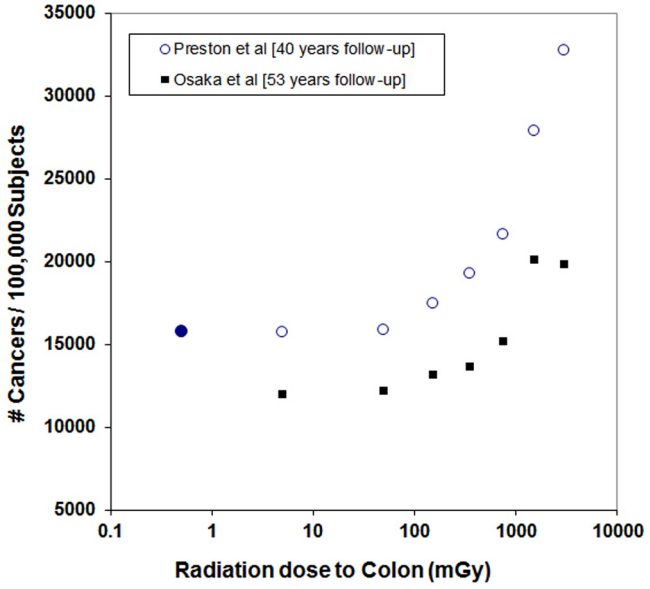

Fig. 3. Number of solid cancers per 100,000 subjects in Hiroshima and Nagasaki, as a function of dose. Data taken from Table 4, Preston et al. [24] and Table 9, Ozasa et al. [25]. The solid circle represents cancer rate in people who were not in the cities at the time of the bombing (from Preston et al.).

about 0.085 Gy. However this model did not fit significantly better than a linear model".

4. BEIR VII – risk models

4.1. EAR, ERR and LAR risk models

In order to generate the appropriate risk models and factors to be used in estimating cancer risks at low doses, the BEIR VII committee relied heavily on analysis done by the RERF on the atomic bomb survivors. The committee utilized two competing cancer risk models that were developed by the RERF– the Excess Relative Risk (ERR) model and the Excess Absolute Risk (EAR) model.

The ERR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0. This is the model that was used by an earlier BEIR V committee and it assumes that the excess risk of cancer is proportional to the baseline cancer incidence, i.e. the ERR is the same for a Japanese and a U.S. or European population. This would be a useful model to predict cancer from ionizing radiation in a Japanese population living in war time conditions, but may not be as applicable to other ethnicities living under different conditions.

The EAR is the rate of disease in an exposed population minus the rate of disease in an unexposed population. This model is more suited if there are significant differences (ethnicity, diet, etc.) between the reference population and the population under investigation. However it assumes that the baseline cancer incidence does not influence the rate of additional cancers induced by ionizing radiation.

Both models allow one to calculate the risk of cancer at a given time after exposure. Hence their value depends on the age and sex of the subject at the time of exposure. So the risk of cancer to a 30-year old subject who received 1 Gy at age 10 will be different from that of a 60-year old subject who received the same dose at age 40. In order to calculate the lifetime risk of cancer from that exposure, a third model is employed called the Lifetime Attributable Risk (LAR). The LAR is essentially the summation of the ERR or EAR estimate of cancer risk for each year after exposure out to an expected lifespan of ~80 years. Hence it is dependent upon the risk model, organ of interest, and the age and sex of the subject at the time of exposure. In addition, the BEIR VII committee incorporated several additional factors such as latency period from exposure to first risk of cancer (5 years for solid cancers), and the dose and dose rate effectiveness factor, which is discussed in more detail below.

In deciding which risk model to use, the BEIR VII committee faced two dilemmas. The first one was the large discrepancy between risk factors from medical studies and atomic bomb survivor studies, as described above. This highlights the uncertainties that the committee faced in estimating the risk factor for a single organ.

The second dilemma in estimating radiation risk is the lack of correlation between the EAR and ERR models. Fig. 4 shows the relationship between the LAR calculated using the EAR and ERR models based on data presented in Table 12-5A (BEIR VII, page 279). Each data point represents a different cancer for males and females. For some organs there is reasonable agreement. For example, the LARs for colon cancer in males are 260 and 180 based on the ERR and EAR model respectively (EAR and ERR are in units of cancers/mixed population of 100,000 exposed to 0.1 Gy). By comparison, the LARs for liver cancer in females are 9 and 85 based on the ERR and EAR models respectively – a factor of ~9 times larger. To generate a single estimate of LAR from these very different estimates of EAR and ERR, the BEIR VII committee opted to create a final risk model in the form

$$\text{Final Risk model} = x.\text{ERR} + (1 - x).\text{EAR}$$

where the factor x was determined subjectively by the committee. The BEIR VII report states that "the resulting range of plausible values for lifetime risk is consequently labeled a subjective confidence interval to emphasize its dependence on opinions in addition to direct numerical observations" (BEIR VII, page 278). In addition the report states that "because of the various sources of uncertainty it is important to regard specific estimates of LAR with a healthy skepticism, placing more faith in a range of possible values" (BEIR VII, page278).

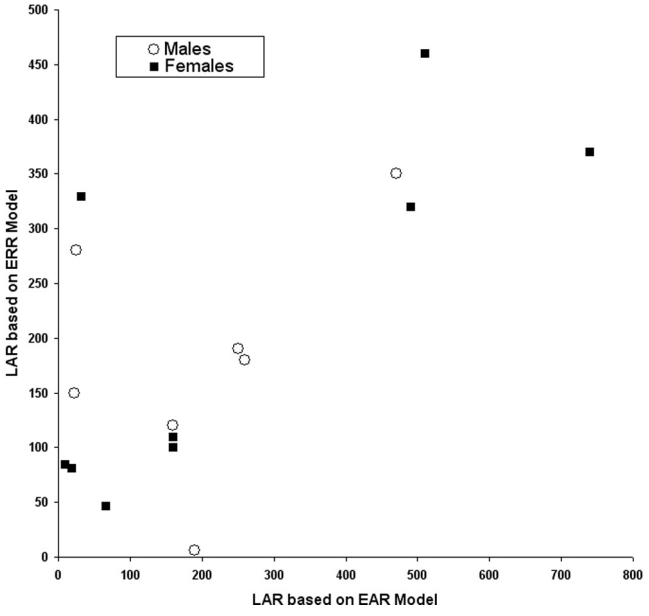

Fig. 4. Correlation between Lifetime Attributable Risk (LAR) of solid cancer incidence, based on application of the Excess Relative Risk (ERR) model, and the Excess Absolute Risk (EAR) model. Cancer incidence is per 100,000 persons of mixed ages exposed to 0.1 Gy. Each data point represents a different organ or site. [Reproduced with permission, from Hendee W R, O'Connor M K. Radiation risks of medical imaging: Separating fact from fantasy. Radiology 2012;264:312–321.]

4.2. Dose and dose-rate effectiveness factor

It is generally accepted that at low doses and low dose-rates, the effects of ionizing radiation are reduced relative to what is observed at high doses or dose rates [26,27]. The magnitude of this reduction is usually described by a parameter called the dose and dose-rate effectiveness factor (DDREF). What is considered low dose and low dose-rate is a matter of debate. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) defined low dose as doses below 100 mGy and low dose rate as being less than 0.1 mGy/minute averaged over 1 h [28], which would encompass all medical imaging procedures and background radiation [29]. The BEIR VII committee chose a value of 1.5 for the DDREF, however Ruhm et al. [26] commented that "*there is compelling evidence in ..... animal data that protracted exposures are associated with less risk than acute exposures. A range of models suggest ..... that DDREF from protracted exposures is between 2.0 and infinity*". More realistically, values of the DDREF derived from studies at the molecular and cellular level support a large (2–30) DDREF [27]. Use of a DDREF of greater than 1 effectively converts the LNT into a linear-quadratic or biphasic model. Values of DDREF greater than 5–10 would essentially negate the validity of the LNT and move closer to a threshold model.

4.3. Exposure in utero

There is a paucity of data on cancer mortality on subjects who were exposed *in utero*. The limited data presented in BEIR VII on the atomic bomb survivors who were irradiated *in utero* suggested that risk estimates for the fetus do not differ significantly from that observed for survivors exposed during the first 5 years of life (BEIR VII, page 151).

5. BEIR Report and AAPM/HPS/UNSCEAR policy statements

As a committee operating under the auspices of the National Academy of Sciences, their report carries significant scientific weight. Many of the assumptions, hypotheses and subjective decisions used to generate risk estimates in the BEIR VII report are buried deep within this 400-page report and are absent from the summary statement and key tables. As a consequence many investigators, clinicians and scientists fail to appreciate the scientific weakness of the risk estimates generated therein. Annex 12D of the report provides a simple to use chart that enables one to calculate the lifetime risk of cancer incidence and mortality for a given amount of radiation, with no warning on the myriad of assumptions and hypotheses that form the basis of this chart.

Analytical decisions made by BEIR committees often resulted in significant changes in estimation of radiation risk. For example, values of LAR from the BEIR VII report increase by an order of magnitude over these reported in the BEIR III and BEIR V reports, due mainly to a decision to switch from use of a linear-quadratic fit to a linear fit. Such a dramatic change in LAR based on analysis of essentially the same dataset underscores the uncertainty in estimate of cancer risk from ionizing radiation. This large uncertainty and the sensational nature of many recent studies predicting large numbers of future cancers from medical imaging procedures [2,5] has led several national and international organizations to issue statements denouncing the practice of multiplying small hypothetical risk estimates by large populations to come up with a large number of cancer deaths. Listed below are the key statements from the Health Physics Society, the American Association of Physicists in Medicine and UNSCEAR [30–32].

"The Health Physics Society recommends against quantitative estimation of health risks below an individual dose of 5 rem (50 mSv) in one year, or a lifetime dose of 10 rem (100 mSv), above that received from natural sources. For doses below 5–10 rem (50–100 mSv) risks of health effects are either too small to be observed or are nonexistent." [30].

The AAPM statement included the following "Risks of medical imaging at patient doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures." [31].

In a 2012 report, UNSCEAR issued a similar statement [32] stating "In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation. This is because of the uncertainties associated with the assessment of risks at low doses, the current absence of radiation-specific biomarkers for health effects and the insufficient statistical power of epidemiological studies. Therefore, the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels." For reference, UNSCEAR has defined worldwide background as between 2 and 13 mSv/year.

6. Future direction

After over 50 years of cumulative research, continued use of the LNT model applied to an ever diminishing population of survivors of Hiroshima and Nagasaki is unlikely to yield results that differ significantly from what is already known. Future research should now be focused on a better understanding of the effects at a biological level. A recent study by Behjati et al. [33] has shown that ionizing radiation generates distinctive mutational signatures that explain its carcinogenic potential. They identified two genomic imprints of ionizing radiation. One was an enrichment of deletions and the second was the presence of an exceedingly rare type of rearrangement of the DNA, called balanced inversion. If further work in this area confirms these findings it would enable identification of radiation-induced cancers based on their mutational signature. This would allow future studies to easily confirm or refute the validity of the last 50 years of data on the stochastic effects of ionizing radiation, and hard facts would replace hypothetical estimates!

7. Conclusion

The main source of data for the BEIR VII risk estimates are the survivors of the Japanese A-bomb explosions. This was a population living under war-time conditions and differing greatly in ethnicity from the present day European and U.S. populations. Despite over 50 years of intensive study, data from the Japanese studies is still inconclusive on any effects of ionizing radiation at doses below ~100 mSv. Scientists and clinicians looking to the BEIR VII report for guidance on risk estimation should be aware of the limitations of the data and the assumptions, hypotheses and subjective decisions used by the BEIR VII committee in generating risk estimates. Position statements by the Health Physics Society, American Association of Physicists in Medicine, and UNSCEAR support the conclusion that the risk estimates in the BEIR VII report should not be

used for estimating cancer risks from low doses of ionizing radiation. A reasonable case can be made that, considering the most conservative of these position statements (UNSCEAR), for imaging procedures with associated effective doses below the upper limit of natural background radiation (~13 mSv), the practice of associating any risk estimate should be discontinued as scientifically unsound.

Conflict of interest

The author has no relevant conflicts of interest with respect to this work.

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