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Threshold doses and circulatory disease risks

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Abstract–Tissue reactions (deterministic effects) become manifest either early or late after doses above a threshold dose, which is the basis for recommended dose limits for avoiding such effects. Threshold doses have been defined for comparative purposes at 1% incidence of an effect, although the choice of incidence level may be scenario-dependent in practice. Latency time before manifestation is related to cell turnover rates and tissue complexity. In general, threshold doses become lower for longer follow-up times because of the slow progression of injury before manifestation, particularly after lower doses. Radiosensitive individuals may contribute to low threshold doses, which would provide a safety margin for the majority of a population. A threshold dose of 0.5 Gy was proposed for radiation-induced circulatory disease, after acute or chronic exposures, in the International Commission on Radiological Protection *Publication 118*. However, more recent meta-analyses of low-dose population studies suggest that, if a linear dose-incidence is assumed, the risk of some types of circulatory disease after doses <0.5 Gy or <10 mGy day^{-1} may be positive and similar to that for induced cancer. Animal studies show that doses >2 Gy induce the expression of inflammatory and thrombotic molecules in endothelial cells. This causes progressive loss of capillaries in the heart and leads to reduced perfusion, myocardial cell death, and fibrosis. However, doses <1 Gy inhibit both inflammatory cell adhesion to endothelial cells and the development of atherosclerosis in mice. Different mechanisms of injury at low and high doses preclude the simple extrapolation of risk on a linear-quadratic basis from acute to chronic exposures.

Keywords: Radiation biology; Circulatory disease; Tissue reactions; Deterministic effects; Threshold doses

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1. THRESHOLD DOSE

A threshold dose for a given effect can be defined as a dose below which the effect does not occur. That dose is often difficult to determine, but is the basis for recommended dose limits pertaining to tissue reactions. One way in which epidemiological evidence for a threshold can be assessed is by examination of the lowest dose at which a statistically significant positive dose–response can be detected. This is subject to uncertainties due to constraints on sample sizes and to the particular model used to fit the data. In the present context of tissue reactions, the 'threshold dose' is defined as estimated dose for 1% incidence (ED_1), denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation (ICRP, 2007, 2012). Although ED_1 is not a true threshold in the sense of the effect not occurring at all, it was considered appropriate for comparative purposes among tissue types. The use of a smaller level than ED_1 would entail a greater extrapolation of response frequencies to even lower doses, with concomitant greater uncertainties attached to the value. The use of a higher level would have less uncertainty in the value, but it would be even further from the 'true' threshold. When these threshold doses are used for protection purposes, the context should be considered carefully. An incidence of 1% or even more of a serious tissue reaction may be an acceptable risk in the radiotherapy of a life-threatening tumour in a cohort of 100–1000 cancer patients, but unacceptable in a fit worker or public population of 10,000 to millions unless the injury is readily correctable such as in the case of induced cataract by lens replacement.

The estimation of ED_1 may be complicated by substantial baseline levels of specific tissue effects or diseases that develop with ageing in the absence of radiation exposure, e.g. cataracts and circulatory disease. In these cases, ED_1 refers to effects just starting to rise above the baseline levels in unirradiated, age-matched individuals. In the case of circulatory disease, it refers to a dose that would increase the already high natural incidence or mortality by only 1%. ED_1 does not imply that no biological effects occur at lower doses; it merely defines the dose above which a specified effect becomes clinically apparent in a small increasing percentage of individuals. The incidence then rises with increasing dose to form a sigmoid dose–response relationship.

Note that the frequency of highly radiosensitive individuals in the general population is considered to be considerably below 1%, and such a population may contribute to a low threshold dose. Also, children appear to be more sensitive than adults to the induction of circulatory disease (e.g. Tukenova et al., 2010). In addition, various biological response modifiers given after exposure can provide dose-modifying factors of 1.1–1.5 for various types of tissue reactions occurring in experimental animal systems (ICRP, 2012). It is hoped that, in the future, some of these modifiers may be found to be helpful in increasing threshold doses in human populations.

2. LATENCY INTERVALS AND RADIATION RISKS

Early tissue reactions after radiation exposure generally have a well-defined latency and expression period that is related to the turnover time of the tissue. In contrast, the majority of late reactions progress and increase in frequency with increasing time. In this late phase, the first reactions to manifest are found after higher doses, and more reactions occur later after lower doses. Hence, threshold doses for specific levels of late tissue reactions are not absolute, and may decrease with increasing follow-up time as more reactions appear after the lower doses. Thus, the thresholds should be quoted as pertaining to a specified time after exposure. A review of many different clinical datasets demonstrated that the development of the incidence of late normal tissue injury occurred with approximately exponential kinetics after high radiation doses, which could be quantified as the percentage of patients at risk of developing a specific effect per year (Jung et al., 2001). This annual percentage risk remained relatively constant with increasing time after irradiation regarding a specific late effect, but it varied between tissues, e.g. 5% year^{-1} for dermal injury, and 12–14% year^{-1} for injury in bladder and ileum after pre-operative radiotherapy for rectal cancer. Most of the data reviewed showed annual increases in incidence up to 10 years maximum follow-up, but some studies showed an increasing incidence of late injury to 20, 25, and 30 years follow-up for some tissues. This indicates that very long follow-up times are needed to assess the accumulated expression of injury over a lifetime.

Also, the exponential kinetics implied that a random process might be involved in the occurrence of late radiation reactions (Jung et al., 2001). In addition, a study of patient-related vs stochastic components of variability for late blood vessel telangiectasia in paired bilateral irradiated areas of skin found that for a given dose-fractionation schedule, patient-related factors explained 81–90% of the patient-to-patient variation in telangiectasia level. The remaining 10–19% was explained by stochastic effects (Safwat et al., 2002). Hence, there is some evidence, albeit quite limited to date, for a stochastic component in tissue responses to radiation. This was also alluded to in the UK Health Protection Agency report on circulatory disease after radiation exposure (HPA, 2010):

> *Were the involvement of a stochastic process to be demonstrated convincingly, it would have significant implications with respect to radiation risk coefficients. However, atherosclerotic disease is a multifunctional disorder and all aspects of its biology need to be considered in relation to causal factors. We do not consider that the available evidence justifies consideration of a stochastic component as being established, although it remains as a possibility. Clearly, further work is needed to establish whether or not radiation can induce transformation of smooth muscle cells to a plaque-type phenotype, whether this induction is a stochastic process, and whether it plays a significant role in atherogenic development. (HPA, 2010).*

3. LOW DOSES AND CHRONIC DOSE RATES

Although higher accumulated total doses would generally be expected to be tolerated after protracted/chronic exposures than after acute exposures, similar threshold doses would be expected if the risk at doses up to the threshold dose was governed by single-hit irreparable injury, with no split-dose repair, slow repair, or cell repopulation effects differentially involved at very low dose levels or low dose rates. Alternatively, the mechanisms of injury may be different as a function of dose and dose-delivery pattern. In that case, it would probably be fortuitous if threshold doses were found to be similar, and statistical uncertainties may also be reflected in this conclusion.

4. CIRCULATORY DISEASE

The most recent analysis of circulatory disease mortality in the atomic bomb survivors showed a near-curvilinear dose–response curve at 20 years follow-up (since exposure in 1945) and a threshold dose consistent with the above-mentioned value of 0.5 Gy (Fig. 1). However, between 20 and 58 years follow-up, the dose–response curve became near-linear with no threshold, consistent with the prediction from biological evidence and human data for blood vessel telangiectasia (Turesson, 1989) that threshold doses may decrease with increasing time after exposure. It is recognised that this is a general conclusion, and the various types of circulatory disease have different shapes of dose–response curve (Takahashi et al., 2013). Also of note is that the general shapes of the dose–response curves in terms of excess relative risk (ERR) for circulatory disease mortality in the two follow-up periods were similar to those for mortality from all solid cancers, with the values of ERR for all circulatory diseases being four to five times less than the values for all solid cancers over the range of doses up to 3 Gy (Fig. 1).

A systematic review and meta-analysis of circulatory disease mortality from low-level radiation was carried out for 10 medical, occupational, and atomic bomb survivor studies, where doses were <0.5 Gy or <10 mGy day^{-1} (Little et al., 2012). A short 5-year latency followed by a constant ERR with further time after exposure, and a linear-no-threshold response, were assumed. The excess population risk for all circulatory diseases combined was 2.5–8.5% Sv^{-1}, which was of the same order as the cancer risk of 4.2–5.6% Sv^{-1} for these populations, indicating their similar importance at these low doses.

Animal studies have contributed knowledge in terms of dose–effect relationships and mechanisms of injury. For example, several studies have been performed using genetically modified ApoE–/– mice, which have a five-fold increased level of cholesterol and a predisposition to atherosclerosis. A single dose of 4 Gy or 20×2-Gy fractions delivered over 4 weeks accelerated atherosclerosis with an inflammatory thrombotic plaque phenotype (Hoving et al., 2008). Also, doses of 0.025–0.5 Gy, at an early or late stage of disease, impacted variously on the development of atherosclerosis (Mitchel et al., 2011). In addition, cardiac exposure to 0.2 Gy induced

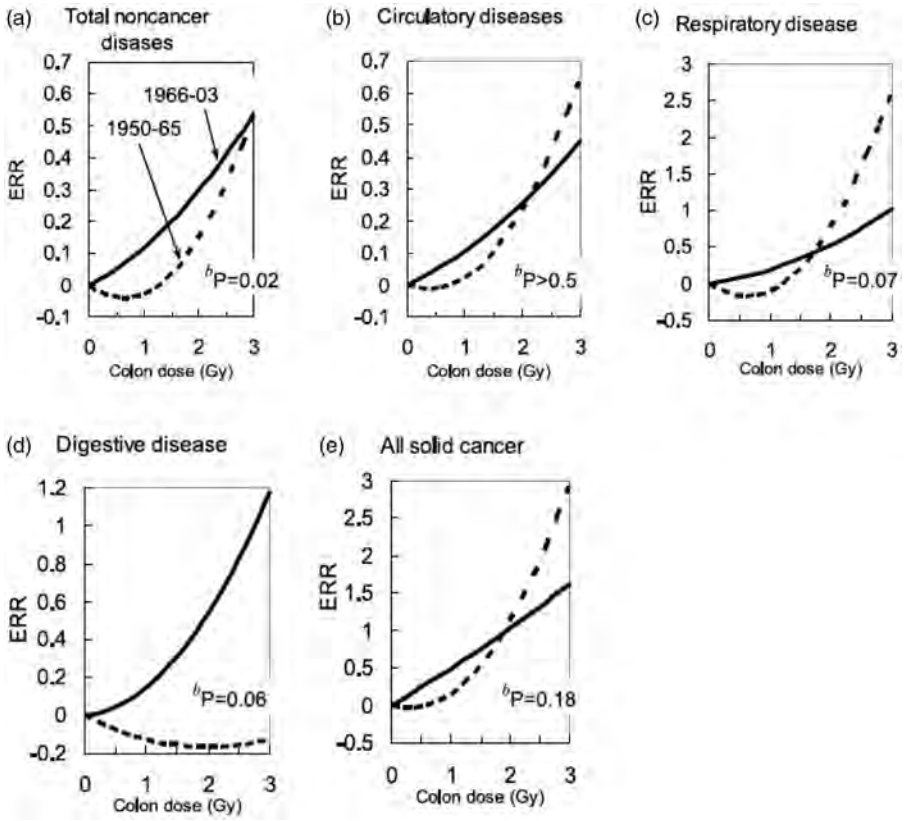

Figure 1. Dose–response curves for the early period (1950–1965, dashed curves) and the later period (1966–2003) for circulatory diseases in the atomic bomb survivors. ^{b}P values denote the significance of the difference between the two curves. ERR, excess relative risk. Source: Ozasa et al. (2012), figure reprinted with permission from *Radiation Research* and Dr Kotaro Ozasa.

significant physiological, histopathological, cellular, and molecular heart alterations, with mild functional impairment and early pro-inflammatory polarisation of macrophages (Monceau et al., 2013). Another model system is the stroke-prone spontaneously hypertensive rat, considered to be a good model of cerebrovascular diseases caused by severe hypertension and arteriosclerosis because the overall vascular changes in the brain and other organs are consistent with those observed in malignant hypertension (Takahashi et al., 2013).

A succinct summary of the mechanisms operating as a function of dose was given by Stewart (2012):

> *In large arteries, doses of ≥8 Gy, combined with elevated cholesterol, initiate atherosclerosis and predispose to the formation of inflammatory, unstable lesions, which are prone to*

rupture and may cause a fatal heart attack or stroke. Doses of ≥2 Gy induce the expression of inflammatory and thrombotic molecules in endothelial cells. In the heart, this causes progressive loss of capillaries and eventually leads to reduced perfusion, myocardial cell death, and fibrosis. Doses <1 Gy inhibit inflammatory cell adhesion to endothelial cells and inhibit the development of atherosclerosis in mice. It seems likely that mechanisms other than accelerated atherosclerosis are responsible for cardiovascular effects after low total-body exposures of radiation (e.g. impaired T-cell immunity or persistent increase in systemic cytokines).

Research in this topic is continuing and notable is the large European-Union-funded project on radiation-induced circulatory disease (www.procardio.eu), which follows a previous project (www.cardiorisk.eu). This support is helping to increase knowledge in this area.

Circulatory disease was recognised some years ago as one of the important non-cancer diseases induced by radiation, and several review articles were published covering epidemiology, dose–response relationships, and potential mechanisms of the effects (e.g. Hendry et al., 2008; UNSCEAR, 2008; Darby et al., 2010; HPA, 2010; ICRP, 2012). In 2013, with the accrual of more information on this subject, some new review articles were published. These cover, for example, epidemiology of circulatory effects after low-dose exposures (Little, 2013), circulatory disease induced by higher doses received from radiotherapeutic exposures and strategies for intervention (Stewart et al., 2013), a workshop report from the Radiation Effects Research Foundation (Japan) on many aspects of radiation-induced circulatory disease including directions for future research (Takahashi et al., 2013), and a review by consultant experts to the International Atomic Energy Agency also aimed at formulating new research questions in this area (Wondergem et al., 2013). Clearly, the topic of radiation-induced circulatory disease has become recognised as very important in protection and medical scenarios.

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