RADIATION RESEARCH 151, 225–229 (1999)
0033-7587/99 $5.00

COMMENTARY

Does Fractionation Decrease the Risk of Breast Cancer Induced by Low-LET Radiation?

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Brenner, D. J. Does Fractionation Decrease the Risk of Breast Cancer Induced by Low-LET Radiation? *Radiat. Res.* 151, 225–229 (1999).

Whether fractionation decreases the risk of breast cancer induced by low-LET radiation is a question of some importance. Analyses of the data for TB cohorts who were exposed to multiple fluoroscopies show an apparently similar breast cancer risk compared with those for the acutely exposed A-bomb survivors. However, the fluoroscopy cohorts were subjected to very much lower-energy photons (60–80 kVp) compared with the A-bomb survivors; the increased RBE associated with the low photon energies to which these fluoroscopy cohorts were exposed suggests that, in comparison to the risk estimates for the A-bomb survivors, the risk estimates from the X-ray fluoroscopy cohorts are increased because of the lower-energy X rays and decreased by a similar amount due to fractionation, resulting in an overall *apparent* equality of risk. Thus the results from the most powerful epidemiological data sets available for assessing breast cancer risks after fractionated exposure to low-LET radiation (the fluoroscopy cohorts) are quite consistent with a lower radiation risk for a fractionated exposure in comparison to an acute exposure. In general, for any cancer site, estimates of the dose-rate effectiveness factor (DDREF) generated by comparing the results for A-bomb survivors with those for the TB fluoroscopy cohorts should probably be roughly doubled from their apparent values because of the increased RBE of the fluoroscopy X rays.

INTRODUCTION

One of the most important issues in radiation protection is the effect of dose protraction. Specifically, while most of the data from which we derive risk estimates for low-LET radiation are from the acutely exposed A-bomb survivors, we are primarily interested in the effects of protracted or highly fractionated exposures over long periods.

For low-LET radiation, there is much radiobiological evidence that protraction lowers the risk of oncogenesis (e.g. *1–4*). However, the epidemiological evidence for solid tumors is far more limited, and various committees have recommended different values for the so-called dose-rate effectiveness factor (DDREF), which is the factor by which risk estimates appropriate for high dose rate should be reduced to be applicable to prolonged exposures. Based primarily on comparisons of carcinogenesis after high- and low-dose-rate exposures at low doses in mice (*3*), DDREFs recommended by various committees for induction solid tumors by low-LET radiation are in the range of 2–10 (*4–6*).

In this context, the two tuberculosis (TB) fluoroscopy cohort studies from Canada (*7, 8*) and Massachusetts (*9–11*) are of considerable importance. Two large cohorts of women (~13,000 in the Canadian cohort, ~2,500 in the Massachusetts cohort) were exposed to well-separated multiple low-dose fractions (mean ~90 fractions, mean breast dose per fraction ~8 mGy) of low-energy X rays over an average of about 3 years. Thus a comparison between risk estimates for breast cancer mortality derived from the acutely exposed A-bomb survivors and from these TB fluoroscopy cohorts should provide some measure of the effects of dose protraction. While there are other groups who were subjected to fractionated exposure and who have been assessed for cancer risks, these other groups are smaller [e.g. ~600 exposed in the Rochester postpartum mastitis cohort (*12*)], and so there is less opportunity to draw quantitative conclusions.

For the end point of radiation-induced *lung* cancer, a reduced risk was indeed observed in the fluoroscopy cohorts compared with that in the acutely exposed A-bomb survivors (*11, 13*). On the other hand, most of the recent studies comparing *breast* cancer risks in the TB cohorts with those for the A-bomb survivors have concluded that the observed risks are similar; i.e., there is little or no effect of dose rate (*7, 9, 10*). An exception is a recent study by Howe (*8*) on breast cancer incidence in the Canadian TB cohort, in which a comparison with A-bomb data did suggest a protraction-related decrease in risk.

A conclusion that dose protraction does not decrease the risk of radiation-induced breast cancer would be in disagreement with the recommendations of the ICRP (*6*), UN-

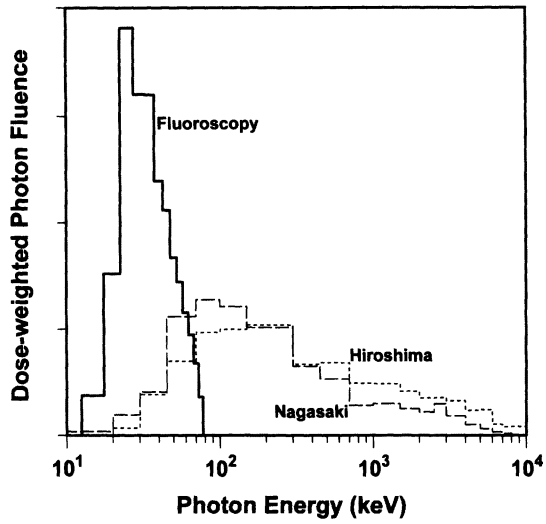

FIG. 1. Fluence energy spectra, $\phi(E)$, for the various photon fields discussed here. Shown are normalized spectra $E\ \phi(E)\ \mu_{en}(E)/\rho$, where $\mu_{en}(E)/\rho$ is the mass-energy absorption coefficient at photon energy E; this representation is such that the area under the curves delimited by any two photon energies is approximately proportional to the fraction of dose deposited by photons in that energy range. Solid line: 80 kVp X rays from a tungsten target, typical of those used in fluoroscopic examinations given to tuberculosis patients (*14–16*). Also shown are photon spectra incident on survivors at Hiroshima (short dash, ground distance 1.5 km) and Nagasaki (long dash, ground distance 1.9 km). A-bomb spectra courtesy of Dr. W. Woolson, Science Applications Inc., San Diego.

SCEAR (*4*) and the BEIR V Committee (*5*). If protraction does not affect the risk of breast cancer induced by low-LET radiation, the consequences would be far-reaching. In addition to considerations of mechanisms, the current system of radiological protection (*6*) includes a DDREF of 2 to account for the decreased effects of a protracted exposure. If one of the most important radiation-related cancers does not show a protraction effect, in a radiation protection setting the DDREF might need to be reduced to 1, with the result that both occupational and public exposure limits would need to be halved.

It is argued here, however, that there is another factor that needs to be considered in comparing the fluoroscopy cohorts and the A-bomb survivors. Specifically, it is suggested that the much lower photon energy spectrum to which the fluoroscopy cohorts were exposed would result in an increase in biological effect of the order of 1.6–1.9 relative to the γ rays to which the A-bomb survivors were exposed. When this is taken into account, instead of an apparent equality of risk for breast cancer, the data for the fluoroscopy cohorts indicate a decrease in risk for breast cancer compared to the A-bomb survivors. This decrease is of much the same order as might be expected from fractionation. More generally, this argument suggests that, for any end point, an *apparent* DDREF, estimated from a *prima facie* comparison between the A-bomb survivors and the fluoroscopy cohorts, should be roughly doubled because of the different photon energies in the two cases.

Figure 1 compares a typical X-ray spectrum to which the members of the TB fluoroscopy cohorts were exposed with γ-ray energy spectra at relevant distances at Hiroshima and Nagasaki. The representation is such that the area under the curves delimited by any two photon energies is approximately proportional to the fraction of dose deposited by photons in that energy range. For example, the majority of the dose delivered absorbed by A-bomb survivors came from photons above 150 keV, while all of the dose delivered to the fluoroscopy cohorts came from photons with energy below 80 keV, and the majority of this dose from photons with energy below 30 keV.

It is, however, now well established that the RBE of photons increases with decreasing photon energy (*17*). This observation is both well established experimentally and well understood mechanistically. The phenomenon is understood theoretically, in that as the energy of the photons decreases, the energy of the secondary electrons emitted in the photon interactions decreases, with a corresponding increase in stopping power (linear energy transfer, LET). For example, the LET of a 30 keV secondary photoelectron is around 1 keV/μm, which is considerably larger than, for example, the LET of 0.2 keV/μm of a 500 keV secondary electron.

That moderately low doses of low-energy X rays (with mean energies comparable to those in the fluoroscopy exposures) have an increased biological effectiveness has been demonstrated in a variety of different biological systems, for example by Virsik *et al.* (*18*) and Sasaki *et al.* (*19*) for chromosome aberrations in human lymphocytes; by Verhaegen and Vral (*20*) and Kwan *et al.* (*21*) for micronuclei in human lymphocytes; by Hering *et al.* (*22*), Zeitz *et al.* (*23*) and Marchese *et al.* (*24*) for clonogenic survival in cells of human origin; by Arslan *et al.* (*25*) for cell survival and chromosome aberrations in rodent cells; and by Bistrovic *et al.* (*26*), Hoshi *et al.* (*27*), Spadinger and Palcic (*28*), and Ling *et al.* (*29*) for cell survival in rodent cells.

In assessing the low-energy photon RBEs published in the literature, it is important to note that the increased biological effectiveness of low-energy X rays is a low-dose effect—as the dose per fraction increases, the difference in effectiveness between any two types of radiation will decrease (*17, 30*). Scalliet and Wambersie (*30*) reviewed the experimental data up to 1987 on the RBE of ^{125}I photons (mean energy ~28 keV) compared to high-energy γ rays; they concluded that, whereas the RBE of ^{125}I relative to γ rays was around 1.2 at high doses and dose rates, at low doses and dose rates RBE values were in the range 1.5–2.4.

Given that the RBE will decrease as the dose per fraction increases, it is important to quantify whether the dose per fraction delivered to the fluoroscopy cohorts was sufficiently low that a higher RBE would be expected, or high enough that such effects would be expected to be small. Within the framework of the linear-quadratic formalism [where the risk from a single dose D of a given radiation

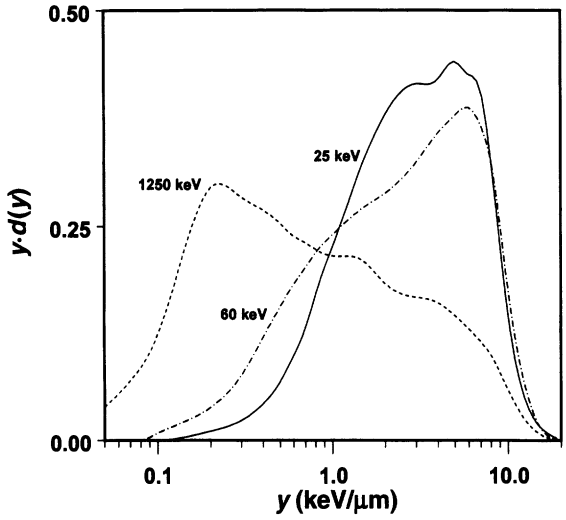

FIG. 2. Measured microdosimetric energy deposition spectra in 1-μm site sizes, for various monoenergetic photons [after Kliauga and Dvorak (*32*)]. The representation is such that the area under the curves delimited by any two lineal energy (y) values is proportional to the fraction of dose deposited by photons in that energy range. As the photon energy increases, there is a major shift in the energy deposition pattern toward lower lineal energy (y) values.

is related to $\alpha D + \beta D^2$ (*31*)], the RBE of the low-energy X rays relative to γ rays will approach unity at doses per fraction, d, such that $d \gg \alpha/\beta$, and will approach its maximum value when $d < \alpha/\beta$. The average dose per fraction for the fluoroscopy cohorts was ~8 mGy (*7–11*), which may be compared with an estimate of α/β for γ-ray-induced breast cancer in mice of 23 mGy (*2*); it may be concluded that the dose per fraction was sufficiently low that an increased RBE would be expected.

METHODS

The large differences in energy deposition patterns which underlie the differences in biological effect with changing photon energy can be quantified through energy deposition spectra in micrometer-sized targets, as shown in Fig. 2. Specifically, the energy deposition pattern in individual cells can be quantified (*33*) in terms of the distribution of lineal energy (y, the microdosimetric correlate of LET), defined as the energy deposited (in this case by an incident photon) in a given target size divided by the mean path length of the target.

At low doses, the energy distribution patterns, $d(y)$, in individual cells or substructures of cells must determine the biological effect of one radiation relative to that of another. Such a situation follows if the initial lesion for cancer is related to energy deposition in a single cell, a notion supported by the known monoclonal origin of many breast cancers (e.g. *34–36*). In such a situation, all that changes, for a given dose, from radiation to radiation is the distribution of energy deposited in target cells—which is exactly the information in a microdosimetric spectrum. For a given low dose, the response, R (per unit dose), of a biological end point, ε, to a given radiation quality, i, can be written (*37*)

$$R_{\varepsilon i} = \int r_\varepsilon(y)\, d_i(y)\, dy, \qquad (1)$$

where $d_i(y)$ is the normalized distribution of dose in lineal energy for radiation type i (see Fig. 2), and $r_\varepsilon(y)$ is the relative effect for end point ε as a function of lineal energy. In other words, cells respond with a response function $r_\varepsilon(y)$ (independent of the radiation but characteristic of the end point) to a range of energy depositions $d_i(y)$ (independent of the end point but characteristic of the radiation), producing a total response $R_{\varepsilon i}$. Equation (1) is valid for predicting relative biological effects at low doses even if the mechanism of cancer induction involves interaction between autonomous cells, or promoting factors, as long as these processes are independent of radiation quality.

The first quantitative estimates of the biological response function $r_\varepsilon(y)$ were for the end point of chromosomal aberrations in human lymphocytes (*37*), and the function has also been extracted for the end points of HPRT mutation in human fibroblasts (*38*) and oncogenic transformation in C3H 10T½ cells (*39*). Varma and Zaider (*40*) have also derived this function for cellular inactivation end points. The International Commission on Radiation Units and Measurements (ICRU) has also published a "consensus" $r(y)$ function (*17*).

In the following, microdosimetric spectra, $d(y)$, appropriate for the A-bomb radiations and for TB fluoroscopy were estimated. These were then folded (see Eq. 1) with several biological response functions $r_\varepsilon(y)$ to obtain estimates of the low-dose relative effectiveness of the fluoroscopy X rays compared to the A-bomb γ rays.

The energy deposition spectra, $d(y)$, for these different photon fields were calculated based on previously measured spectra for monoenergetic photons (*32*), using the following relationship (*41*):

$$d(y) = \int E\, N(E)\, d(y;E)\, \mu_{en}(E)/\rho\, dE, \qquad (2)$$

where $N(E)$ is the fluence of photons at energy E, and $\mu_{en}(E)/\rho$ is the mass-energy absorption coefficient in breast-equivalent material of density ρ at photon energy E. $d(y;E)$ is the normalized spectrum of lineal energy depositions for monoenergetic photons of energy E; these spectra for monoenergetic photons were taken from measurements (*32*, see Fig. 2) in a 1-μm equivalent-diameter wall-less proportional counter, which includes data for 12, 25, 36, 60, 140, 320, 662 and 1250 keV monoenergetic photons. For the A-bomb exposures, where there were significant numbers of high-energy photons, it was assumed that the lineal-energy spectrum $d(y;E)$ does not change significantly as the photon energy increases from 1.25 to 10 MeV (*42*). Interpolation between photon energies was achieved using a two-dimensional interpolation scheme described by Akima (*43*).

RESULTS

Three different biological response functions, $r_\varepsilon(y)$ (see Eq. 1), were used which have previously been evaluated in the literature, derived from measurements of induction of exchange-type chromosomal aberrations (*17, 37*), of mutation at the *HPRT* locus (*38*), and of *in vitro* oncogenic transformation (*39*). Two different X-ray spectra (80 kVp and 60 kVp, both with 1.5 mm Al filtration) were also used, corresponding to the energy range that was used on the fluoroscopy cohorts (*14, 15*).

For each end point, Table 1 shows the low-dose relative effectiveness of the TB fluoroscopy X rays normalized to unity for Hiroshima A-bomb γ rays. It is clear that the different biological end points give a fairly consistent picture of the relative biological effectiveness of the different radiations (data row 1 compared to row 2 compared to row 3), and that there is no major variation in biological effectiveness over the X-ray energy range that was used for TB fluoroscopy (data column 3 compared to column 4); there is also no major variation in biological effectiveness of the photons between Hiroshima and Nagasaki (data column 1 compared to column 2). Most importantly, there is a significant increase in the biological effectiveness of the X rays used for TB fluoroscopy compared with the γ rays

TABLE 1
Calculated Low-Dose Relative Risks for Fluoroscopy-Energy X Rays and A-Bomb Gamma Rays

End point	Hiroshima bomb (1.5 km ground distance)	Nagasaki bomb (1.9 km ground distance)	80 kVp X rays	60 kVp X rays
Exchange-type chromosome aberrations (*17, 37*)	1	1.06	1.61	1.63
Mutation at *HPRT* locus (*38*)	1	1.04	1.72	1.76
In vitro oncogenic transformation (*39*)	1	1.06	1.90	1.96

incident on A-bomb survivors (data columns 3 and 4 compared to columns 1 and 2).

DISCUSSION

Based on the three end points analyzed here (induction of exchange-type chromosomal aberrations, mutation at the *HPRT* locus, and *in vitro* oncogenic transformation), it is estimated that the fluoroscopy X rays would be around 1.6 to 1.9 times more biologically effective at low doses compared to A-bomb γ rays. It follows that an apparent equality between breast cancer risk estimates from the TB cohorts and from the A-bomb survivors suggests a DDREF of this same factor, 1.6 to 1.9. These values are comparable to the currently recommended value for the DDREF of 2 (*6*). Thus it is likely that, in comparison to the risk estimates for the acutely exposed A-bomb survivors, the breast cancer risk estimates from the X-ray fluoroscopy cohorts are increased because of the lower-energy X rays and are decreased by a similar amount due to fractionation, resulting in an overall *apparent* equality of risk.

The calculations reported here do not prove definitively that a reduction in the risk estimates for radiation-induced breast cancer is warranted for fractionated exposures compared to acute exposures, and other interpretations of the data are possible. However, these considerations do show that the most powerful epidemiological data sets available for assessing breast cancer risks after fractionated exposure (the fluoroscopy cohorts) are quite consistent with a lower radiation risk for a fractionated exposure in comparison to an acute exposure and, arguably, are inconsistent with a DDREF of 1. The conclusion that fractionation probably decreases the risk of radiation-induced cancer is consistent with most (though not all) available animal and *in vitro* data (*1–4, 44–45*).

More generally, for any cancer site, the increased biological effectiveness of the fluoroscopy X rays compared to A-bomb γ rays suggests that the *apparent* DDREF for that cancer site that is established by a *prima facie* comparison between the fluoroscopy cohorts and A-bomb survivors should probably be about doubled. This would be true, as we have discussed, for breast cancer, where a *prima facie* evaluation of the DDREF of 1 might reasonably be doubled, but would also be true for other end points, such as lung cancer, where the *apparent* DDREF is already greater than one; the analysis here suggests that such apparent DDREFs should also be doubled.

ACKNOWLEDGMENTS

This work was supported by NIH grants CA77285 and CA24232 and DOE grant DE-FG02-98ER62686.

Received: December 23, 1997; accepted: September 29, 1998

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