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Routine screening mammography: how important is the radiation-risk side of the benefit–risk equation?

D. J. BRENNER†*, S. G. SAWANT‡, M. P. HANDE†, R. C. MILLER§, C. D. ELLISTON†, Z. FU¶, G. RANDERS-PEHRSON† and S. A. MARINO†

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Abstract.
The potential radiation hazards associated with routine screening mammography, in terms of breast cancer induction, are discussed in the context of the potential benefits. The very low energy X-rays used in screening mammography (26–30 kVp) are expected to be more hazardous, per unit dose, than high-energy X- or γ-rays, such as those to which A-bomb survivors (from which radiation risk estimates are derived) were exposed. Based on *in vitro* studies using oncogenic transformation and chromosome aberration end-points, as well as theoretical estimates, it seems likely that low doses of low-energy X-rays produce an increased risk per unit dose (compared with high energy photons) of about a factor of 2. Because of the low doses involved in screening mammography, the benefit–risk ratio for older women would still be expected to be large, though for younger women the increase in the estimated radiation risk suggests a somewhat later age than currently recommended—by about 5–10 years—at which to commence routine breast screening.

1. Background

There has been much recent debate about the benefits of routine screening mammography (e.g. Olsen and Gøtzsche 2001, Miettinen *et al.* 2002). There has been rather less discussion about possible radiation-related risks associated with these examinations, specifically the risk of radiation-induced breast cancer, although some risk–benefit analyses have been reported (Howe *et al.* 1981, NCRP 1986, Feig *et al.* 1995, Law 1995, Jansen and Zoetlief 1995).

Glandular doses from screening mammography are low, typically around 3 mGy (Young and Burch 2000, Kruger and Schueller 2001) of 26–30 kVp low-energy X-rays. A particular issue here, however, is that these very low-energy X-rays are expected to be more hazardous, per unit dose, than high-energy X- or γ-rays (i.e. those on which radiation risk estimates are based, such as from the Hiroshima and Nagasaki A-bombs). The underlying biophysical reason for the expected increase in biological effectiveness of these lower-energy X-rays is that they set in motion slower secondary electrons, with correspondingly higher LET (Brenner and Amols 1989, Kellerer 2002).

In this regard, Frankenberg *et al.* (2002) reported data on *in vitro* oncogenic transformations frequencies induced by 29-kVp X-rays relative to 'conventional' 200-kVp X-rays suggesting that the low-energy X-rays used in screening mammography are considerably more biologically effective. This conclusion echoes some earlier calculations on this subject (Brenner and Amols 1989) and a variety of earlier experimental data for chromosome aberration induction (see below).

An increase in the relative biological effectiveness (RBE) of low-energy mammographic X-rays compared with high-energy photons is of relevance in assessing the risk side of the benefit–risk equation for routine mammography. This is because radiation-related risks are currently calculated based on studies of populations (A-bomb survivors and women who received multiple fluoroscopies) exposed to high-energy photons (Howe *et al.* 1981, NCRP 1986, Feig *et al.* 1995, Law 1995, Jansen and Zoetlief 1995).

Of course, the significance of any enhancement in the biological effect of mammographic X-rays depends on its magnitude: Virsik and Harder (1978) estimated a low-dose RBE of 1.2 ± 0.8 for dicentric induction by 30-kVp relative to 150-kVp X-rays, and Verhaegen and Vral (1994) estimated a low-dose RBE of 1.6 ± 0.9 for micronucleus induction by 14-kVp relative to 350-kVp X-rays, while Sasaki *et al.* (1989) estimated a low-dose RBE of 0.83 ± 0.79 for dicentric aberration induction by 14.6 keV relative to 200 kVp X-rays. More recently, Frankenberg *et al.* (2002) have presented data for an *in vitro* oncogenic transformation endpoint with an estimated low-dose RBE of 4.7 ± 4.2 for 29-kVp relative to 200-kVp X-rays.

2. Experimental observations

We measured *in vitro* onogenic transformation frequencies in $C_3H10T½$ cells, induced by mono-energetic X-rays in the 15–25 keV range (Marino

*Author for correspondence; e-mail: djb3@columbia.edu
†Center for Radiological Research, Columbia University, 630 West 168th Street, New York, NY 10032, USA.
‡Amgen, Inc., Thousand Oaks, CA, USA.
§Radiological Society of North America, Oak Brook, IL, USA.
¶Brookhaven National Laboratory, Upton, NY, USA.

et al. 2002), produced at the X23A3 beamline (Long *et al.* 2001) at the Brookhaven National Synchrotron Light Source. Oncogenic transformation data for 15.2 keV monoenergetic X-rays are shown in figure 1. Using linear–quadratic fits (figure 1) to the low-dose data, we estimated a low-dose RBE ($\alpha_{15keV}/\alpha_{662keV}$, see legend to figure 1) of 1.96 ± 0.78 for 15.2-keV X-rays relative to high-energy 662-keV ^{137}Cs γ-rays. While these experiments are still in progress for this and other end-points, in no case did we estimate a low-dose RBE (defined, as above, as the ratio of α terms) of >1.5 relative to 250-kVp X-rays (0.2 mm Cu, 1 mm Al external filtration), or >2.5 relative to ^{137}Cs γ-rays.

These fairly modest RBE estimates are consistent with the earlier experimental data (see above), as well as theoretical estimates (Brenner and Amols 1989) of 1.3 (versus 250-kVp X-rays) and 2.0 (versus γ-rays at Hiroshima and Nagasaki), for the low-dose RBE of 23-kVp filtered X-rays. These enhancements are comparatively small because the differences in energy deposition patterns between the high- and low-energy photons are relatively subtle (Brenner and Amols 1989, Kellerer 2002, Verhaegen and Castellano 2002).

If the risks per unit dose of mammographic X-rays are indeed about twice as large as those from the radiations at Hiroshima and Nagasaki, this would be of significance in assessing the benefit–risk balance for screening mammography. For example, figure 2 shows the age-dependent benefit–risk ratio, as estimated in the NCRP Report 85 (1986) for yearly mammogram examinations for 5 years, each producing a 2-mGy glandular dose. Here the 'benefit' is assumed to be a 10% decrease in mortality rate, and the excess relative risk of radiation-related breast cancer was appropriately derived from studies of the Japanese A-bomb survivors. Now, if it were assumed that low doses of mammographic X-rays are twice as hazardous, per unit dose, as the Japanese A-bomb γ-rays, then the mammographic benefit–risk ratios would be decreased, by this same factor of 2.

As illustrated in figure 2, such a reduction in the benefit–risk ratio could have implications about the age at which commencement of annual breast screening is recommended. For example, commencing routine screening at age 40 (American Cancer Society recommendation, Leitch *et al.* 1997) corresponds to reaching some minimum benefit–risk ratio (numerically equal to

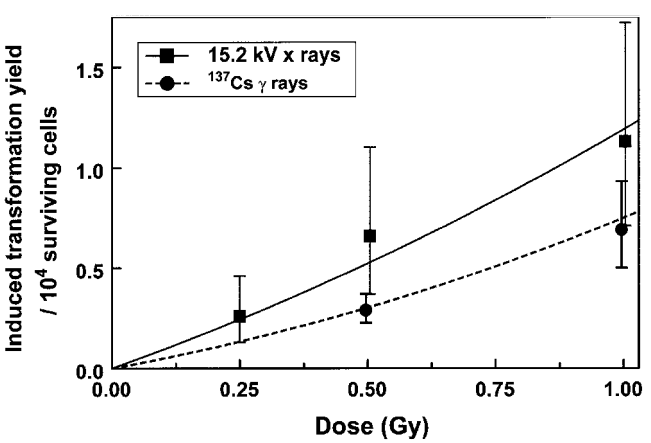

Figure 1. Induced oncogenic transformation frequencies (and 68% confidence limits) in $C_3H10T½$ cells, measured as a function of the dose of 662 keV ^{137}Cs γ-rays and 15.2 keV monoenergetic X-rays. The 15.2-keV monoenergetic X-rays were produced on the X23A3 beamline at the Brookhaven National Synchrotron Light Source (NSLS, Long *et al.* 2001), with dosimetry as described by Marino *et al.* (2002). For clarity, only low-dose data points are shown. The curves represent fits to the full data set using the models $TF_{15keV} = \alpha_{15keV} D + \beta D^2$ and $TF_{662keV} = \alpha_{662keV} D + \beta D^2$, where $\alpha_{15keV} = 0.90 \pm 0.15\,Gy^{-1}$ and $\alpha_{662keV} = 0.46 \pm 0.11\,Gy^{-1}$; here TF is the induced transformation frequency and D is the dose.

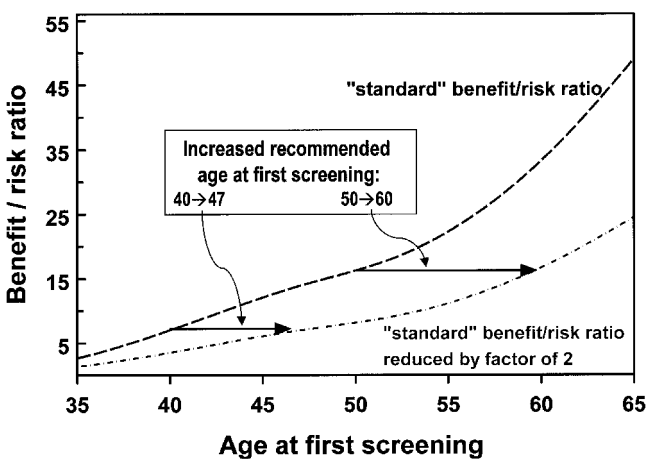

Figure 2. (upper curve) Estimated benefit–risk ratio for yearly mammographic screening examinations for 5 years, assuming a glandular dose of 2 mGy per examination (NCRP 1986). The benefit is assumed to be a 10% reduction in breast cancer mortality rate, and the excess relative risk for radiation-induced breast cancer was assumed to be $2.2 \times 10^{-4}\,mGy^{-1}$. Further details of the calculation are given in NCRP (1986). (lower curve) Corresponding benefit–risk ratio in which the estimated radiation risk is doubled to account for an increased risk per unit dose of about 2 for low-energy mammographic X-rays. Arrows indicate the increase in age at which a given benefit–risk ratio would be attained, assuming the radiation risk were doubled; they suggest that recommended starting ages for routine mammography might reasonably be increased by 5–10 years if the radiation risk from mammographic X-rays was twice as large as previously assumed. Note that the absolute values of the benefit–risk ratio shown in this figure are dependent on how the benefit is defined and quantified, and are less meaningful in this context than the temporal displacement between the two curves.

7 in figure 2). If the benefit–risk ratio were halved because the radiation risk was twice that previously estimated, then the age at which this same benefit–risk ratio is reached would be increased, in this case from age 40 to 47 (figure 2). If annual screening were recommended from age 50 (NIH Consensus Panel 1997), doubling the radiation risk while keeping fixed the benefit–risk ratio for commencement of screening would imply an increase in the recommended age to begin screening, from age 50 to about 60 (figure 2). Similar quantitative conclusions are obtained if other estimates of the age-dependent benefit–risk ratio for mammographic screening (e.g. Law 1995) are re-analysed by doubling the radiation risk.

3. Conclusions

There is evidence that low-energy X-rays as used in mammographic screening produce an increased biological risk per unit dose relative to higher-energy photons. At low doses, the increased risk appears to be in the range of a factor of 2. Thus it is extremely unlikely that the radiation risk alone could prove to be a 'show stopper' regarding screening mammography because, for older women, the benefit is still likely to outweight considerably the radiation risk. For women <50 years of age, however, this increase in the estimated radiation risk might indicate a somewhat later age than currently suggested, by about 5–10 years, at which to recommend commencement of routine breast screening.

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