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# Mutations in the BRCA1 gene: implications of inter-population differences for predicting the risk of radiation-induced breast cancers

R. CHAKRABORTY[1] AND K. SANKARANARAYANAN[2]*

[1] *Human Genetics Center, University of Texas School of Public Health, PO Box 20334, Houston, TX 77225, USA*
[2] *Department of Radiation Genetics and Chemical Mutagenesis, Leiden University Medical Centre, Sylvius Laboratories, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands*

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**Summary**

The effects of cancer predisposition and increased tumorigenic radiosensitivity of the predisposed genotypes on radiation cancer risks (in the general population and in sisters and first cousins of affected probands) are studied using an autosomal dominant model of cancer predisposition and radiosensitivity. The model assumes that the predisposing alleles, which confer enhanced tumorigenic radiosensitivity, are incompletely penetrant. In addition, the model also allows for sporadic cancers, unrelated to the predisposing locus. The predictions of the model are illustrated using current estimates of BRCA1 mutant gene frequencies; the estimates of the strength of predisposition and radiosensitivity differentials used are based on animal and human studies. It is shown that, unless both the strength of predisposition and radiosensitivity differential are large (say, $>$ 100-fold in comparison with normal homozygotes), (i) the effect of risk heterogeneity on cancer risk is marginal; (ii) dose-dependent radiation effect remains virtually the same as in a homogeneous irradiated population that has no predisposed subgroups; (iii) for the same radiation dose, relatives of affected probands show an enhancement of cancer risks; and (iv) most extra cancers in relatives can be attributed to radiosensitivity differentials. This simple model can give an upper bound of the effect of risk heterogeneity on radiation-induced breast cancer risks even when the cumulative breast cancer risk is age-dependent. Further, our model predicts that the benefits of mammography outweigh the risks.

## 1. Introduction

Estimates of lifetime risk of breast cancer, one of the most common cancers in women, show considerable racial/ethnic differences (e.g. Parkin *et al.*, 1993; Ziegler *et al.*, 1994). Recent figures suggest that in the USA, 1 in 8 women develops this neoplasm, while for Japanese women the corresponding lifetime risk is approximately 1 in 50 (American Cancer Society, 1995). Initial estimates indicated that 5–10% of all breast cancers in western women may be due to inherited predisposition (Claus *et al.*, 1991). The cloning of the BRCA1 (Miki *et al.*, 1994; Futreal *et al.*, 1994) and BRCA2 (Wooster *et al.*, 1995; Tavtigian *et al.*, 1996) genes and subsequent worldwide studies (reviewed in Szabo & King, 1997) have now established the important contribution of mutations in these two genes to breast and ovarian cancers. In most populations, about 6–10% of all breast and ovarian cancers unselected for family history occur in carriers of germline mutations in these genes (Szabo & King, 1997): in Israel, the attributable fraction is somewhat higher (8·9% for BRCA1 mutations and 4·5% for BRCA2 mutations: Abeliovich *et al.*, 1997). More recently, Newman *et al.* (1998) have estimated that only 3·3% of US Caucasian female breast cancers have disease-related mutations at the BRCA1 gene.

Studies of high-risk families show that the risk of breast and/or ovarian cancers varies with age and depends on which of the two genes (BRCA1 or BRCA2) is mutated (e.g. Narod *et al.*, 1995; Whittemore *et al.*, 1997; Ford *et al.*, 1998). For most populations (other than Icelandic) the frequency of BRCA1 mutations is 1·5- to 2·0-fold higher than that of BRCA2 mutations (Szabo & King, 1997). For the

* Corresponding author. Telephone: +31 71 5276155. Fax: +31 71 5221615.

US population, based on a case–control design family study, Whittemore *et al.* (1997) estimated that (i) a dominant mutant allele with a frequency of 0·0014 can explain the observed familial aggregation of breast and ovarian cancers and (ii) for the mutant gene carriers the risk for breast cancer is 42·3% by age 50 years and 73·5% by age 80 years; these figures are 34·5- and 10·8-fold higher than those of non-carriers for the corresponding ages. In a number of large series of young Ashkenzai Jewish women, the combined population frequency of carriers of three specific mutations is about 2·5% (BRCA1 185delAG, 1·0%; BRCA1 insC, 0·1%; and BRCA2 delT, 1·4%: see Levy-Lahad *et al.*, 1997).

In this paper, we examine the implications of these findings in the context of exposures to ionizing radiation in unrelated women as well as in sisters of affected probands. The rationale for this rests on observations from human epidemiological studies and animal experiments that lend credence to the view that carriers of mutations in familial cancer genes may be at a higher risk of cancers induced by radiation (e.g. Land *et al.*, 1993; Tokunaga *et al.*, 1994; Storer *et al.*, 1988; Hino *et al.*, 1993; Kemp *et al.*, 1994; reviewed in Sankaranarayanan & Chakraborty, 1995). Should this be true of BRCA mutation carriers, they may be at a higher risk of breast cancers induced by radiation than those who do not carry these mutations. In turn, this will affect estimates of radiation-induced cancer risks. Additionally, the question of benefit versus risks of screening by mammography may arise.

Using an autosomal dominant model of cancer predisposition and radiosensitivity differential we show that (i) unless the strength of cancer predisposition and radiosensitivity differentials are both very substantial, the increase in the risk of radiation-induced breast cancers in a heterogeneous population (compared with one that does not have breast cancer predisposed and radiosensitive subgroups) is small; (ii) enrichment of predisposing mutant alleles in relatives (e.g. sisters) of affected probands also does not affect this conclusion and (iii) even when the mutant gene frequency is high, as is the case with Ashkenazi Jewish women, the benefits of mammography outweigh the risks.

## 2. A model of cancer predisposition and radiosensitivity

Details of the one-locus, two-allele, autosomal dominant model used to evaluate the combined effects of cancer predisposition and radiosensitivity are given in Chakraborty & Sankaranarayanan (1995) and Chakraborty *et al.* (1997, 1998). Table 1 presents the definition of the parameters and risk measures used and Fig. 1 shows how cancer risks are affected by radiation for each genotype at the susceptibility locus.

The assumptions of the model are: (i) the frequencies of the three genotypes in the population conform to Hardy–Weinberg expectations; (ii) the predisposed genotypes ($AA$ and $Aa$) also have enhanced tumorigenic radiosensitivity; (iii) the probability with which the $Aa$ genotypes confer cancer susceptibility and radiosensitivity (i.e. penetrance) is $\theta$; and (iv) only a fraction $\pi$ of individuals in the population have cancers due to their predisposing genotypes; in the remainder $(1-\pi)$ the cancers are sporadic (i.e. unrelated to their genotypes).

For individuals of the $(1-\pi)$ group, cancer risk at radiation dose $D$ will be $R_0(1+\beta D)$, the same as that for those who do not have the mutant allele ($A$), or for whom the dominant allele is not fully penetrant (which occurs with probability $1-\theta$). Thus, the total breast cancer risk in the irradiated population (at dose $D$ Gy) is given by

$$\begin{aligned} R_T(D) &= (1-\pi)\,R_0(1+\beta D)+\pi[(P_{AA}+\theta P_{Aa})\,R_0\,R_p \\ &\quad \times(1+\beta D R_i)+\{(1-\theta)\,P_{Aa}+P_{aa}\}\,R_0(1+\beta D)] \\ &= R_0[(1+\beta D)+\pi(P_{AA}+\theta P_{Aa}) \\ &\quad \times\{R_p(1+\beta D R_i)-(1+\beta D)\}]. \end{aligned} \tag{1}$$

Before any further use of (1) recall that in this while $\pi$ represents the fraction of individuals in the general population who are genetically susceptible to cancer, this parameter alone is not enough to examine the effects of different exposures to radiation between individuals (or families). This is so because, in (1), the radiation dose $D$ appears also in a term that is free of $\pi$. Of course, as this equation indicates, the larger the value of $\pi$, the greater is the risk of cancers when individuals are exposed to any given dose ($D$) of radiation.

The three risk measures of interest, namely, the relative risk [$RR(D)$], attributable fraction [$AF(D)$], and the proportion of $AF(D)$ that is due to enhanced radiosensitivity alone [$\alpha(D)$], are given by (derived in Chakraborty *et al.*, 1997, 1998):

$$\begin{aligned} RR(D) &= \frac{R_T(D)}{R_0(1+\beta D)} \\ &= 1+\pi(P_{AA}+\theta P_{Aa})\left[\frac{R_p(1+\beta D R_i}{1+\beta D}-1\right], \end{aligned} \tag{2}$$

$$\begin{aligned} AF(D) &= \frac{R_T(D)-R_0(1+\beta D)}{R_T(D)} \\ &= \frac{\pi(P_{AA}+\theta P_{Aa})\,[R_p(1+\beta D R_i)-(1+\beta D)]}{(1+\beta D)+\pi(P_{AA}+\theta P_{Aa}) \\ &\qquad +[R_p(1+\beta D R_i)-(1+\beta D)]}, \end{aligned} \tag{3}$$

and

$$\begin{aligned} \alpha(D) &= \frac{R_T(D)-R_B(1+\beta D)}{R_T(D)-R_0(1+\beta D)} \\ &= \frac{\beta D R_p(R_i-1)}{R_p(1+\beta D R_i)-(1+\beta D)}, \end{aligned} \tag{4}$$

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Table 1. *Notation and interpretation of parameters of the autosomal dominant model of cancer predisposition and radiosensitivity*

| Notation | Definition/interpretation |
|---|---|
| $AA$, $Aa$, $aa$ | Genotypes ($A$ is the dominant allele, which confers cancer predisposition as well as radiosensitivity to the genotypes $a$, the normal allele) |
| $p$, $q$ | Gene frequencies ($p$ for the $A$ allele, and $q$ for the $a$ allele; $p+q=1$) |
| $\theta$ | Penetrance; the probability with which the $Aa$ genotype confer higher susceptibility and radiosensitivity (see Fig. 1) |
| $\pi$ | Fraction of individuals in the population whose cancers are due to their predisposing genotypes |
| $\phi_0$, $\phi_1$, $\phi_2$ | Identity-by-descent probabilities of a relative sharing 0, 1 or 2 alleles, respectively, at the susceptibility locus with an affected proband |
| $R_0$ | Sporadic cancer risk in the population in the absence of radiation (which also applies for the low-risk genotypes ($aa$ and a fraction $(1-\theta)$ of $Aa$ genotype; see Fig. 1). In the irradiated population the sporadic cancer risk is $R_0(1+\beta D)$ |
| $R_B$ | Background cancer risk in an unirradiated population in which some genotypes are genetically predisposed ('susceptibles', [**S**]) while others are not ('non-susceptibles' [**NS**]) |
| $R_p$ | Factor by which the background cancer risk is increased in the [**S**] relative to [NS] genotypes. In the present context it is the relative risk for $AA$ and a fraction of $Aa$ genotypes in comparison with the cancer risk ($R_0$) in $aa$ individuals |
| $D$ | Radiation dose (in Gy) |
| $\beta$ | Slope of the radiation dose effect curve; it denotes the excess relative risk coefficient for genotype $aa$, which is also approximately the relative risk coefficient in the general population. Thus, cancer risk in [**NS**] individuals exposed to a dose $D$ of radiation is $R_0(1+\beta D)$ |
| $R_i$ | Strength of radiosensitivity differential; a factor by which the slope of the radiation dose effect curve is increased in [**S**] individuals; i.e. multiplier of the excess relative risk for [**S**] individuals, yielding cancer risks in [**S**] individuals at dose $D$ of radiation equal to $R_0(1+\beta D R_i)$ |
| $R_T(D)$ | Total cancer risk at dose $D$ in an irradiated population consisting of [**S**] and [**NS**] genotypes |
| $AF(D)$ | Fraction of cancers at dose $D$ in an irradiated population attributed to [**S**] genotypes; i.e. $1-[R_0(1+\beta D)/R_T(D)]$ |
| $\alpha(D)$ | Proportion of total cancers at dose $D$ in an irradiated population that is due to enhanced radiosensitivity alone |
| $RR(D)$ | Relative risk $= R_T(D)/[R_0(1+\beta D)]$ |
| Gy | Gray; unit of absorbed radiation dose (equivalent to 100 rads in earlier terminology) |
| Sv | Sievert unit; unit of radiation used in radiological protection. It is the absorbed dose averaged over a tissue or organ and weighted for the radiation quality of interest. For radiations such as X-rays and gamma-rays, 1 Gy = 1 Sv |

in which $R_B$, the background breast cancer risk (in an unexposed population) in the presence of susceptible individuals in the population, is given by

$$R_B = R_0[1+\pi(P_{AA}+\theta P_{Aa})(R_p-1)]. \quad (5)$$

For unrelated individuals, the genotype frequencies, $P_{AA}$, $P_{Aa}$ and $P_{aa}$ may be approximated by their Hardy–Weinberg expectations ($p^2$, $2pq$ and $q^2$, respectively). For a relative of an affected proband, these probabilities will also depend on the degree of relationship of the relatives with the affected proband and the penetrance of the mutant allele(s) (Chakraborty *et al.*, 1998) and are given by

$$P_{AA} = \frac{p^2[\phi_2+\phi_1 p+\phi_0 p^2]+\theta p^2 q[\phi_1+2\phi_0 p]}{}, \quad (6)$$

$$P_{Aa} = \frac{p^2 q[\phi_1+2\phi_0 p]+\theta pq[2\phi_2+\phi_1+4\phi_0 pq]}{p^2+2\theta pq}, \quad (7)$$

and

$$P_{aa} = \frac{\phi_0 p^2 q^2+\theta pq^2[\phi_1+2\phi_0 p]}{p^2+2\theta pq}, \quad (8)$$

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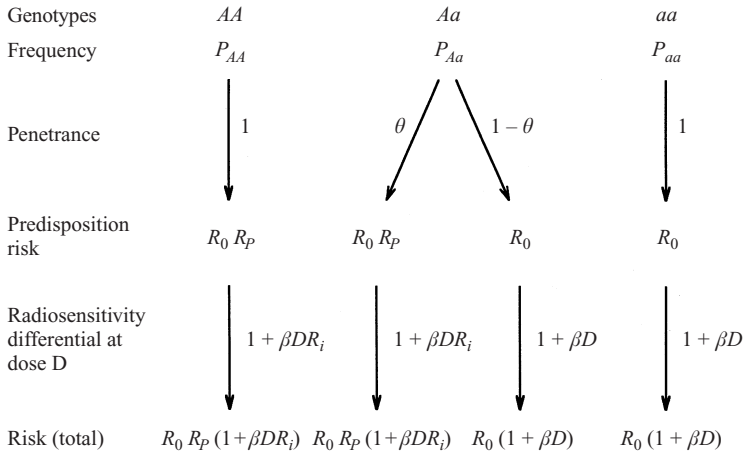


Fig. 1. Schematic diagram of the effects of radiosensitivity differentials, strength of predisposition and incomplete penetrance on individuals of different genotypes.

respectively, where the coefficients $\phi_0$, $\phi_1$ and $\phi_2$ represent the probabilities, that the relatives share 0, 1 or 2 alleles at a locus identical by descent. For unrelated individuals, $\phi_2 = \phi_1 = 0$, and $\phi_0 = 1$; for first cousins $\phi_2 = 0$, $\phi_1 = 1/4$, and $\phi_0 = 3/4$; while for sisters $\phi_2 = 1/4 = \phi_0$, and $\phi_1 = 1/2$. Expressions (6)–(8) can be substituted in equations (2)–(4) for computing the three risk measures for any relative of an affected proband. It is worth noting that the proportion of extra cancers that are due to radiosensitivity alone [$\alpha(D)$] (equation 4), is a function of radiation dose ($D$), the slope of the dose–response curve ($\beta$), radiosensitivity differential ($R_i$), and the strength of predisposition ($R_p$). It does not depend upon the gene frequency ($p$), or the proportion ($\pi$) of cancers that are not caused by the susceptibility locus. The other two risk measures (i.e. $RR(D)$ and $AF(D)$), however, depend on $p$, $\pi$ and $\theta$ as well.

Although the three risk measures are relevant for evaluating cancer risks in an irradiated group (of any biological relative of a proband), the same equations can also be used to study the effect of cancer-predisposing genotypes in the absence of exposure to radiation. This can be done by substituting $D = 0$ in (2) and (3). The radiosensitivity differential ($R_i$) and $\alpha(D)$ are irrelevant when the radiation dose is zero. The quantity $AF(D)$, in this situation, defines the extra cancers that are due to the presence of susceptible genotypes in the population.

## 3. Numerical results for BRCA1 mutation-related and radiation-induced breast cancers

### (i) *Parameter values for non-Jewish Caucasian women*

For non-Jewish Caucasian women, the combined frequency of dominant mutations (gene frequency, $p$) has been estimated to be in the range of 0·0006 to 0·0033 (Claus *et al.*, 1991; Ford *et al.*, 1995; Whittemore *et al.*, 1997). We use the value of $p = 0{\cdot}0014$ (Whittemore *et al.*, 1997), because this is the most recent and the earlier higher estimate ($p = 0{\cdot}0033$; Claus *et al.*, 1991) probably relates to disease-related variants at BRCA1, BRCA2 and other genes. Whittemore *et al.* (1997) also estimated that carriers have a lifetime (at or before 80 years of age) risk ($\theta$) of 73·5% for breast cancers. The strength of the predisposition parameter ($R_p$) of our model approximates the risk ratio in carriers versus non-carriers and is age-dependent. Since the estimate of $\theta = 0{\cdot}735$ refer to cumulative risk at $\leqslant 80$ years of age, we use the risk ratio of 10·8 ($= 0{\cdot}735/0{\cdot}068 = R_p$) as estimated by Whittemore *et al.* (1997). For the proportion of breast cancers attributable to BRCA1 mutations ($\pi$), we use the estimate of 3·3% (Newman *et al.*, 1998).

The effect of radiation in the general population, estimated by the excess risk coefficient ($\beta$) from the A-bomb survivors study is $\beta = 1{\cdot}59$ per Sievert unit (all ages; 95% CI 1·09–2·19; Thompson *et al.*, 1994). For assessing radiosensitivity differentials, data from human studies are limited (Land *et al.*, 1993; Tokunaga *et al.*, 1994). Data from animal studies with tumour suppressor genes such as *p53* in mice (Kemp *et al.*, 1993) and *Tsc2* in Eker rats (Hino *et al.*, 1993) suggest that heterozygotes may be 10 (mice) or 170 (Eker rats) times more sensitive to radiation-induced cancers than normal homozygotes. We use $R_i = 10$ and 200. We included $R_i = 1$ for illustrating the effect of genetic predisposition alone. For radiation dose levels applicable for breast cancer, we used a range of $D = 0$ (for examining the effect of predisposition alone) up to 1·0 Gy.

### (ii) *Parameter values for Ashkenazi Jewish women*

For Ashkenazi Jewish women, we use a gene frequency of 0·0055 corresponding to the BRCA1 185delAG

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Table 2. *Comparison of breast cancer risks in unrelated females and sisters of affected probands in the presence of radiosensitivity and cancer predisposition due to a dominant locus, as a function of radiation dose (D) for parameter values applicable to US Caucasian and Ashkenazi Jewish women*

| | $P = 0{\cdot}0014$, $\theta = 0{\cdot}735$, $\pi = 0{\cdot}033$ | | | | | | $P = 0{\cdot}0055$, $\theta = 0{\cdot}64$, $\pi = 0{\cdot}089$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unrelated | | | Sister | | | Unrelated | | | Sister | | |
| Dose ($D$) in Gy | *RR* | *AF* | $\alpha$ | *RR* | *AF* | $\alpha$ | *RR* | *AF* | $\alpha$ | *RR* | *AF* | $\alpha$ |
| $R_i = 1$, $R_p = 10{\cdot}8$ | | | | | | | | | | | | |
| 0·40 | 1·00 | 0·00 | – | 1·00 | 0·00 | – | 1·01 | 0·01 | – | 1·01 | 0·01 | – |
| 0·50 | 1·00 | 0·00 | 0·00 | 1·00 | 0·00 | 0·00 | 1·01 | 0·01 | 0·00 | 1·01 | 0·01 | 0·00 |
| 0·75 | 1·00 | 0·00 | 0·00 | 1·00 | 0·00 | 0·00 | 1·01 | 0·01 | 0·00 | 1·01 | 0·01 | 0·00 |
| 1·00 | 1·00 | 0·00 | 0·00 | 1·00 | 0·00 | 0·00 | 1·01 | 0·01 | 0·00 | 1·01 | 0·01 | 0·00 |
| $R_i = 10$, $R_p = 10{\cdot}8$ | | | | | | | | | | | | |
| 0·40 | 1·00 | 0·00 | – | 1·00 | 0·00 | – | 1·01 | 0·01 | – | 1·01 | 0·01 | – |
| 0·50 | 1·00 | 0·00 | 0·81 | 1·01 | 0·01 | 0·87 | 1·03 | 0·03 | 0·81 | 1·08 | 0·07 | 0·90 |
| 0·75 | 1·00 | 0·00 | 0·84 | 1·01 | 0·01 | 0·90 | 1·04 | 0·04 | 0·84 | 1·11 | 0·10 | 0·93 |
| 1·00 | 1·00 | 0·00 | 0·85 | 1·01 | 0·01 | 0·91 | 1·04 | 0·04 | 0·86 | 1·13 | 0·11 | 0·94 |
| $R_i = 200$, $R_p = 10{\cdot}8$ | | | | | | | | | | | | |
| 0·40 | 1·00 | 0·00 | – | 1·00 | 0·00 | – | 1·01 | 0·01 | – | 1·01 | 0·01 | – |
| 0·50 | 1·07 | 0·06 | 0·99 | 1·78 | 0·44 | 1·00 | 1·60 | 0·38 | 0·99 | 11·80 | 0·92 | 1·00 |
| 0·75 | 1·08 | 0·07 | 0·99 | 2·14 | 0·53 | 1·00 | 1·74 | 0·42 | 0·99 | 15·86 | 0·94 | 1·00 |
| 1·00 | 1·09 | 0·08 | 0·99 | 2·42 | 0·59 | 1·00 | 1·83 | 0·45 | 0·99 | 18·87 | 0·95 | 1·00 |

$\beta = 1{\cdot}59$/Sv (Thompson *et al.*, 1994) was used for all computations.

and 5382insC mutations, for which the heterozygote frequency is 1·1% (see Levy-Lahad *et al.*, 1997). The proportion of breast cancers due to BRCA1 mutations in this population is also higher ($\pi = 0{\cdot}089$; Abeliovich *et al.*, 1997). For $\theta$ we use 0·64, since the penetrance of BRCA1 mutations for breast and ovarian cancers by 80 years of age is 64% (Levy-Lahad *et al.*, 1997), while Struewing *et al.* (1997) have obtained a value of 56% by age 70 years for breast cancer alone.

For this population the strength of predisposition parameter ($R_p$) is more difficult to predict. The cumulative age-specific risk ratios (carriers of BRCA1 or BRCA2 mutations versus non-carriers) estimated by Struewing *et al.* (1997) range between 7·3 (at age $\leqslant 50$ years) to 4·3 (at age $\leqslant 70$ years). However, Levy-Lahad *et al.* (1997) noted that the BRCA1 mutations have a 2·1-fold higher penetrance than that of BRCA2 mutations. We, therefore, use the same value of $R_p = 10{\cdot}8$ as for the non-Jewish Caucasian women. Likewise, the radiosensitivity-related parameters, $R_i$ and $\beta$, have been assumed to be the same as cited earlier.

### (iii) *Results*

The results obtained using the parameter values discussed above are summarized in Table 2, from which the following observations can be made. First, in non-Jewish Caucasian women, in the absence of radiation exposure ($D = 0$; left half of the first row of each panel of Table 2), the presence of predisposing mutations does not increase breast cancer risk. This holds for unrelated individuals as well as for relatives of affected probands, as reflected in both *RR* and *AF*.

Secondly, radiation exposure adds additional cancers, and the presence of predisposing mutations causes an increase in the frequency in an absolute sense, but only when the radiosensitivity differential is substantial. In unrelated individuals, even at a dose level of 1 Gy, only a marginal increase of *RR* to 1·09 is expected when $R_i = 200$ and $R_p = 10{\cdot}8$. In sisters of affected women, however, *RR* reaches a value of 2·42 under similar conditions. Consequently, in such women (sisters of affected probands) 59% of extra cancers are attributable to predisposing mutations (i.e. $AF = 0{\cdot}59$).

Thirdly, the $\alpha(D)$—computations show that even when radiosensitivity differential is moderate (say, $R_i = 10$), a substantial proportion of the extra cancers is due to radiosensitivity alone. For example, in unrelated non-Jewish women, for $R_i = 10$, and $R_p = 10{\cdot}8$ at 0·5 Gy dose of radiation, even though the risk ratio [$RR(D)$] is not detectably different from 1, nearly 81% of the extra cancers are due to radiosensitivity, i.e., $\alpha(D) = 0{\cdot}81$, present in the population. In sisters of affected probands, this fraction reaches a level of 87% at the same dose of radiation.

Fourthly, in Ashkenazi Jewish women for whom the mutant gene frequency is nearly four times higher ($p = 0{\cdot}0055$ as opposed to 0·0014) and the proportion of breast cancers due to BRCA1 mutations is 2·7 times higher ($\pi = 0{\cdot}089$ as opposed to 0·033), in the absence

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of radiation, the $RR$ is only marginally higher than 1. In part this is due to the estimated lower penetrance of mutant genes in these women (i.e. $\theta = 0{\cdot}64$ vs $0{\cdot}735$).

Fifthly, in unrelated Jewish women the $RR$ shows a somewhat stronger effect of the predisposing radiosensitive mutant alleles. For example, at a dose of 1 Gy, $RR$ is 1·83 when $R_i = 200$ and $R_p = 10{\cdot}8$. In sisters of affected women in this population the increase in $RR$ is very substantial ($RR = 18{\cdot}87$ under similar conditions). Consequently, in such women (sisters of affected probands) 95% of extra cancers are attributable to predisposing mutations (i.e. $AF = 0{\cdot}95$). Additionally, nearly all extra cancers are due to radiosensitivity differential alone (i.e. $\alpha(D) \simeq 100\%$).

## 4. Implications of the results for a risk–benefit assessment of mammographic screening

### (i) *Synergistic effects of strength of cancer predisposition and radiosensitivity*

The computations shown in Table 2 indicate that the elevation of cancer risks in unrelated individuals as well as in relatives of affected probands largely depends on the frequency of the predisposing alleles in the population and penetrance of the mutant genes. The effects of strength of predisposition ($R_p$) and radiosensitivity differential ($R_i$) are, however, synergistic, as shown in Chakraborty *et al.* (1997, 1998), in which these effects were studied by simultaneously varying these two parameters for given combinations of the others.

Their results show that even for fully penetrant dominant mutations, both $R_i$ and $R_p$ will have to be very large (say, $> 100$) in order for a population to exhibit a substantial elevation of cancer risks due to the risk heterogeneity in the population, compared with an exposed group in which susceptible alleles do not exist. When $R_i > 1$ (and $R_p$ is close to 1) and vice versa, no significant enhancement of radiation cancer risks is expected in the exposed group. These results hold even for close relatives (such as full sisters of affected probands, among whom there is an enrichment of susceptible genes). It can, therefore, be concluded that the current estimates of radiation-induced cancer risks in exposed populations, which do not take into account tumorigenic heterogeneity of radiosensitivity, are probably applicable even for populations where predisposing alleles are more common (e.g. as in Ashkenazi Jewish women).

### (ii) *Implications for mammographic screening*

Given these results, it is instructive to enquire into the risk compared with the benefit of detection of breast cancers by mammography, which involves exposure to small radiation doses (of the order of about 0·001 Gy; Young & Ramsdale, 1993; Mettler *et al.*, 1995) but helps to detect a proportion of these cancers. To estimate the risk compared with the benefit of mammography, we can define a ratio of risk for mammography relative to no-mammography as

$$RR_M = (1-\Psi) + \frac{\beta D[1+\pi(p^2+2\theta pq)(R_p R_i - 1)]}{1+\pi(p^2+2\theta pq)(R_p - 1)}, \quad (9)$$

in which $\Psi$ is the proportion of breast cancers detected by mammography (Chakraborty *et al.*, 1998). This equation implies that when $RR_M < 1$, mammography is beneficial; $RR_M > 1$ indicates additional cancer risks due to mammography.

Table 3 presents some numerical computations that relate to the US non-Jewish Caucasian and Ashkenazi Jewish women. As is evident, with increasing proportions of breast cancers detected, mammography becomes more beneficial (i.e. $RR_M$ is a decreasing function of increasing $\Psi$). When the diagnostic dose is small and, in particular, when $R_i$ and $R_p$ are small, $RR_M$ is nearly equal to the complement of the proportion of cancers detected by mammography.

Table 3. *Risk ratios of breast cancers after mammography relative to non-mammography*

| | $p = 0{\cdot}0014$, $\theta = 0{\cdot}735$, $\pi = 0{\cdot}033$ | | | $p = 0{\cdot}0055$, $\theta = 0{\cdot}64$, $\pi = 0{\cdot}089$ | | |
|---|---|---|---|---|---|---|
| $\Psi$ | $R_i = 1$ | $R_i = 10$ | $R_i = 200$ | $R_i = 1$ | $R_i = 10$ | $R_i = 200$ |
| 0·1 | 0·90159 | 0·09160 | 0·90182 | 0·90159 | 0·90169 | 0·90372 |
| 0·2 | 0·80159 | 0·80160 | 0·80182 | 0·80159 | 0·80169 | 0·80372 |
| 0·3 | 0·70159 | 0·70160 | 0·70182 | 0·70159 | 0·70169 | 0·70372 |
| 0·4 | 0·60159 | 0·60160 | 0·60182 | 0·60159 | 0·60169 | 0·60372 |
| 0·5 | 0·50159 | 0·50160 | 0·50182 | 0·50159 | 0·50169 | 0·50372 |
| 0·6 | 0·40159 | 0·40160 | 0·40182 | 0·40159 | 0·40169 | 0·40372 |
| 0·7 | 0·30159 | 0·30160 | 0·30182 | 0·30159 | 0·30169 | 0·30372 |
| 0·8 | 0·20159 | 0·20160 | 0·20182 | 0·20159 | 0·20169 | 0·20372 |
| 0·9 | 0·10159 | 0·10160 | 0·10182 | 0·10159 | 0·10169 | 0·10372 |

Other parameters used are: $R_p = 10{\cdot}8$, $\beta = 1{\cdot}59$/Sv and $D = 0{\cdot}001$ Gy.

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Even for Ashkenazi Jewish women, for whom the mutant allele frequencies are high ($P = 0{\cdot}0055$), mammography will be generally beneficial (i.e. $RR_M$ is $< 1$).

## 5. Discussion and conclusions

In this paper we have shown that recent molecular data on BRCA1 mutations can be used to assess their impact on radiation-induced cancer risks. The major conclusion is that, unless the strength of predisposition ($R_p$) and radiosensitivity differential ($R_i$) are both high, mutations in such genes do not dramatically enhance radiation-induced cancer risk in unrelated individuals (compared with what is expected in the absence of such gene mutations) in a population exposed to the same dose of radiation. Therefore, unless it is shown that mutations that confer higher risk of breast cancers (such as those at BRCA1 and BRCA2 genes) are also dramatically radiosensitive, they will not contribute much to the amount of radiation-induced cancers, in addition to what will otherwise occur by radiation alone. High gene frequencies and the larger proportion of breast cancers attributable to mutations, of the magnitude observed in Ashkenazi Jewish women, do not alter these conclusions.

The model examined here and the parameters chosen for numerical illustrations are reasonable from genetic considerations. However, epidemiological effects of radiation are far more complex. For example, cumulative risk of breast (and ovarian) cancer is age-dependent (e.g. Ford *et al*., 1998) and the proportion of genetically susceptible women among breast cancer patients depends upon the age of onset. Thus, penetrance coefficient ($\theta$), as well as the proportion of breast cancers due to the susceptibility locus ($\pi$), used in the present model, are truly age-dependent parameters. Our numerical results indicate that the effect of heterogeneity is stronger when either or both of them are increased (Table 2). We deliberately used values of $\pi$ and $\theta$ that correspond to lifetime risk of breast cancers (i.e. $\theta$ larger than that applicable for younger women). Hence, we argue that an age-dependent model should show a weaker effect of genetic heterogeneity than the one illustrated here. Also, it should be noted that in the present model we assumed that radiosensitivity differential (the parameter $R_p$) in the *Aa* heterozygotes works on individuals in whom the mutant allele ($A$) is penetrant (i.e. the risk due to exposure to radiation is enhanced by a factor $R_p$ in a fraction $\theta$ of the *Aa* heterozygotes). This is done for simplicity of the mathematical model, but we argue that it provides a stronger effect of genetic susceptibility to radiation risk, since point mutations alone do not generally affect radiosensitivity as genetic alterations produced by a radiation effect are generally deletions and not point mutations. In principle, while radiosensitivity differential may apply to the locus itself, the enhanced effect of radiation will occur only when radiation would cause deletion in the vicinity of the locus, hampering its normal function. A formal modelling of this would introduce another parameter into the model (such as locus-specificity of deletion) that would have further diluted the effect compared with the ones indicated through our numerical illustrations.

In summary, even though the model used here is simple and does not quantify the age dependence of the effects of radiation, it allows one to quantify the impact of genetic heterogeneity on radiation-induced breast cancers. Unless radiosensitive predisposing mutations are common, and their radiosensitivity differential and strength of predisposition are conjointly dramatic, the radiation dose–response relationship curve, estimated from the general population studies, will not be substantially altered. However, for relatives of affected probands radiation-induced cancer risks may be elevated. Nonetheless, diagnostic mammographic screening, by and large, seems to be beneficial.

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## References

Abeliovich, D., Kaduri, L., Lerer, I., Weinberg, N., Amir, G., Sagi, M., Zlotogora, J., Heching, N. & Peretz, T. (1997). The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. *American Journal of Human Genetics* **60**, 505–514.

American Cancer Society (1995). *Cancer Facts and Figures*. Atlanta, GA: American Cancer Society.

Chakraborty, R. & Sankaranarayanan, K. (1995). Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. II. A mendelian single-locus model of cancer predisposition and radiosensitivity for predicting cancer risks in populations. *Radiation Research* **143**, 293–301.

Chakraborty, R., Little, M. P. & Sankaranarayanan, K. (1997). Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. III. Effects of incomplete penetrance and dose-dependent radiosensitivity on cancer risks in populations. *Radiation Research* **147**, 309–320.

Chakraborty, R., Little, M. P. & Sankaranarayanan, K. (1998). Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. IV. The use of a mendelian single-locus model of cancer predisposition and radiosensitivity to predict cancer risks in relatives of affected individuals. *Radiation Research* **149**, 493–507.

Claus, E. B., Risch, N. & Thompson, W. D. (1991). Genetic analysis of breast cancer in the cancer and steroid hormone study. *American Journal of Human Genetics* **48**, 232–242.

Ford, D., Easton, D. F. & Peto, J. (1995). Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. *American Journal of Human Genetics* **57**, 1457–1462.

Ford, D., Easton, D. F., Stratton, M., Narod, D., Goldgar, P., *et al*. (1998). Genetic heterogeneity and penetrance analysis of BRCA1 and BRCA2 genes in breast cancer. *American Journal of Human Genetics* **62**, 676–689.

Futreal, P. A., Liu, Q., Shattuck-Eidens, D., Cochran, C., Harshman, K., Tavtigian, S., Bennett, L. M., Haugen-Strano, A., Swensen, J., Miki, Y., Eddington, K., McClure, M., Frye, C., Wever-Felhaus, J., Ding, W., Gholami, Z., Soderkvist, P., Terry, L., Jhanwar, C., Berchuck, A., Iglehart, J. D., Marks, J., Ballingler, D. G., Barrett, J. C., Skolnick, M. H., Kamb, A. & Wiseman, R. (1994). BRCA1 mutations in primary breast and ovarian carcinomas. *Science* **266**, 120–122.

Hino, O., Klein-Szanto, A. J. P., Freed, J. J., *et al*. (1993). Spontaneous and radiation-induced renal tumors in the Eker rat model of dominantly inherited cancer. *Proceedings of the National Academy of Sciences of the USA* **90**, 327–331.

Kemp, C. J., Wheldon, T. & Balmain, A. (1994). p-53-deficient mice are extremely susceptible to radiation-induced carcinogenesis. *Nature Genetics* **8**, 66–69.

Land, C. E., Tokunaga, A., Yokuoka, A. & Nakamura, N. (1993). Early-onset breast cancer in A-bomb survivors. *Lancet* **342**, 237.

Levy-Lahad, E., Catane, R., Eisenberg, S., Kaufman, B., Hornreich, G., Lishinsky, E., Shohat, M., Weber, B. L., Beller, U., Lahad, A. & Halle, D. (1997). Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer in breast-ovarian cancer families. *American Journal of Human Genetics* **60**, 1059–1057.

Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P. A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., Bennett, L. M., Ding, W., Bell, R., Rosenthal, J., Hussey, C., Tan, T., McClure, M., Frye, C., Hattier, T., Phelps, R., Haugen-Strano, A., Katcher, H., Yakumo, K., Gholami, Z., Shaffer, D., Stone, S., Bayer, S., Wray, C., Bogden, R., Dayananth, P., Ward, J., Tonin, P., Narod, S., Bristow, P. K., Norris, F. H., Helvering, L., Morrison, P., Rosteck, P., Lai, M., Barrett, J. C., Lewis, C., Neuhausen, S., Cannon-Albright, L., Goldgar, D., Wiseman, R., Kamb, A. & Skolnick, M. H. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* **266**, 66–71.

Narod, S., Ford, D., Devilee, P., Barkardottir, R. B., Lynch, H. T., Smith, S. A., Ponder, B. A. J., *et al*. (1995). An evaluation of the genetic heterogeneity in 145 breast-ovarian cancer families. *American Journal of Human Genetics* **56**, 254–264.

Newman, B., Mu, H., Butler, L. M., Millikan, R. C., Moorman, P. G. & King, M.-C. (1998). Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. *Journal of the American Medical Association* **279**, 915–921.

Parkin, D. M., Muir, C. S., Whelan, S. L., *et al*. (eds.) (1992). *Cancer Incidence in Five Continents*, vol. VI. IARC Scientific Publication no. 120. Lyon: IARC.

Sankaranarayanan, K. & Chakraborty, R. (1995). Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. I. Background. *Radiation Research* **143**, 121–144.

Storer, J. B., Mitchell, T. J. & Fry, R. J. M. (1988). Extrapolation of the relative risk of radiogenic neoplasms across mouse strains and to man. *Radiation Research* **114**, 331–353.

Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., Timmerman, M. M., Brody, L. C. & Tucker, M. A. (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New England Journal of Medicine* **336**, 1401–1408.

Szabo, C. I. & King, M.-C. (1997). Population genetics of BRCA1 and BRCA2. *American Journal of Human Genetics* **60**, 1013–1020.

Tavtigian, S. V., Simard, J., Couch, F., Shattuck-Eidens, M., Neuhausen, S., Marajyer, S., *et al*. (1996). The complete BRCA2 gene and its mutations in chromosome 13q linked-kindreds. *Nature Genetics* **12**, 333–337.

Thompson, D. E., Mabuchi, K., Ron, E., Doda, M., Tokunaga, M., Ochikubo, S., Sigimoto, S., Ikeda, T., Terazaki, M., Izumi, S. & Preston, D. L. (1994). Cancer incidence in atomic bomb survivors. II. Solid tumors, 1958–1987. *Radiation Research* **137**, 817–867.

Tokunaga, M., Land, C. E., Tokuoka, S., Nishimuri, I., Doda, M. & Akiba, S. (1994). Incidence of female breast cancer in atomic bomb survivors. *Radiation Research* **138**, 209–223.

Whittemore, A. S., Gong, G. & Itnyre, J. (1997). Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three US population-based case–control studies of ovarian cancer. *American Journal of Human Genetics* **60**, 496–504.

Wooster, R., Neuhausen, S. L., Mangion, J., Quirk, Y., Ford, D., Collins, N., Nguyen, K., Seal, S., Tran, T., Averill, D., Fields, P., Marshall, G., Narod, S., Lenoir, G. M., Lynch, H., Feunteun, J., Devilee, P., Cornelisse, C. J., Menko, F. H., Daly, P. A., Ormiston, W., McManus, R., Pye, C., Lewis, C. M., Cannon-Albright, L. A., Peto, J., Ponder, B. A. J., Skolnick, M. H., Easton, D. F., Goldgar, D. E. & Stratton, M. R. (1994). Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q120-13. *Science* **265**, 2088–2090.

Ziegler, R. G., Hoover, R. N., Pike, M. C., Hildesheim, A., Nomura, A. M. Y., West, D. W., Wu-Williams, A. H., Horn-Ross, P. L., Rosenthal, J. F. & Hyer, B. (1993). Migration patterns and breast cancer risk in Asian-American women. *Journal of the National Cancer Institute* **85**, 1819–1827.