Carcinogenesis model analysis for breast cancer incidence among atomic bomb survivors and the implications for cancer risk estimate for radiological protection

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INTRODUCTION

Breast cancer incidence is the highest risk due to radiation among atomic bomb survivors. The excess relative risk of the early-onset breast cancer seems to be remarkably high for the youngest age-at-exposure groups. The cancer risk estimate of breast cancer is a current issue in radiological protection. The BEIR V committee used the A-bomb survivor data and the Canadian fluoroscopy study to develop a risk model for breast cancer mortality (1). In this model, the excess relative risk (ERR) for breast cancer mortality is described as a function of dose, years since exposure and age at exposure. Using the same combined data, Howe and McLaughlin developed a simple relative risk model for breast cancer mortality following irradiation: \( RR(d) = 1.0 + 0.52d \exp[-0.10(A-15)] \), where \( d \) is dose in Sieverts and \( A \) is age at exposure (2). Thus, this model assumes that ERR remains constant after exposure. Based on the recently available incidence data, Tokunaga et al. (3) reported that, among women who were younger that 20 years of age at the time of the bomb (ATB), ERR for breast cancer was 13 for women who developed the disease before age 35 in contrast to an ERR of 2 when the disease occurred after age 35.

There are several features of the epidemiology of breast cancer that require special attention during the modelling process. First, the incidence curve for breast cancer shows a flattering around the time of menopause, presumably as a result of declining circulating estrogens following menopause. Second, breast cancer rates have been increasing strongly in Japan, and this increase has been shown to be attributable to birth cohort effects (11). When these cohort effects are properly accounted for, the shape of the age-specific incidence curve in Japan is remarkably similar to the age-specific incidence in western populations, although the absolute incidence rates are much lower in Japan (4). We describe below how we explicitly model these features of breast cancer incidence.

We used a two-stage stochastic model for carcinogenesis to analyze the breast cancer incidence among atomic bomb survivors (5). Our purpose is to examine the dependence of radiation risk on age at exposure using the two-stage model and how to transfer it to other populations for radiological protection.

MATERIALS AND METHODS

The two-stage model has been used in an earlier publication (6) to describe the epidemiology of breast cancer in females. This publication did not consider the effect of ionizing radiation, however. Furthermore, it used an approximate hazard function for the analysis of incidence data. Since the appearance of that paper, several papers have indicated that the use of the approximate hazard function may be inappropriate for the analysis of data. In this paper we used the exact solution to the two-stage model. We also used recent results on the identifiability of parameters of the model (7) to parameterize the model in the most efficient way for likelihood estimation. The mathematical properties regarding the two-stage stochastic model for carcinogenesis have been discussed in detail in the literature (6). The model assumes the number of normal stem cells at time \( t \), \( X(t) \) and the number of initiated (or intermediated ) cell is given by \( \nu(t) \), where \( \nu(t) \) is the first mutation per cell. Then, the initiated cells are generated according to an inhomogeneous Poisson process with intensity \( \nu(t)X(t) \). The initiated cells either divide with the rate \( \alpha(t) \), die (or differentiate) with rate \( \beta(t) \) or divide into one initiated cell and one malignant cell with rate per cell \( \mu(t) \). One malignant cell grows up a clinical detectable tumor after a certain lag time. Our analysis assumes that the hormonal changes associated with menopause occurs at age between 45 and 50 and that the net proliferative rate of intermediate cells changes after the age.

We fitted the model assuming that radiation acts as an initiator and that the rate of radiation-induced mutation and background initiation mutation leading to baseline cancer are additive. We took two age-dependence, not attained age but age at exposure, of the spontaneous process into account. First, age-dependence of spontaneous initiation was expressed by a linear model. We also modeled the age-dependence of spontaneous net growth rate of initiated cells by a linear function. As far as radiation-induced initiation is concerned, we took a stepwise function other than a liner function into account. The likelihood ratio statistic was used for judging model improvement on adding a new parameter.
RESULTS AND DISCUSSION

The menopause-associated age would come around 50 which is age at menopause. The model assuming that changes at age 45, 47.5 or 50 gave a statistically better fit than the time-constant basic model. The age of 45 years at which the hormone changes associated with menopause was fixed in the analyses below since the log-likelihood was higher among three ages.

The analysis did not show that the radiation mutation for the youngest age-at-exposure groups below age 10 was higher than for the older groups. Furthermore, the incidence of female breast cancer in Japan is increasing and the birth cohort effect can be observed in atomic bomb survivors.

Our model assumed that an acute exposure to atomic radiation can only initiate cancers and do not influence other stages of carcinogenesis, whereas spontaneous initiation and promotion are age-dependent to consider birth cohort effects. When these cohort effects are properly accounted for, the shape of the age-specific incidence curve in Japan is remarkably similar to the age-specific incidence in western populations as shown in Fig.1

![Figure 1: Spontaneous breast cancer incidence estimated using our model](image)

Recently, Little and Boice (8) have reported that the excess absolute breast cancer risks between Japanese (atomic bomb survivors) and US women (Massachusetts cohort) are statistically indistinguishable. This fact shows that excess absolute risk is independent of cohorts whereas relative risk is constant for time since exposure. Cohort-related stages in carcinogenesis could be associated with radiation-related stages and consequently it is suggested that an acute exposure is related with promotional stage.

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REFERENCES


