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2005 Phys. Med. Biol. 50 505

(http://iopscience.iop.org/0031-9155/50/3/008)

INSTITUTE OF PHYSICS PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. **50** (2005) 505–520 doi:10.1088/0031-9155/50/3/008

# Use of risk projection models to estimate mortality and incidence from radiation-induced breast cancer in screening programs

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Received 16 August 2004, in final form 12 November 2004
Published 19 January 2005
Online at stacks.iop.org/PMB/50/505

**Abstract**

The authors report on a method to calculate radiological risks, applicable to breast screening programs and other controlled medical exposures to ionizing radiation. In particular, it has been applied to make a risk assessment in the Valencian Breast Cancer Early Detection Program (VBCEDP) in Spain. This method is based on a parametric approach, through Markov processes, of hazard functions for radio-induced breast cancer incidence and mortality, with mean glandular breast dose, attained age and age-at-exposure as covariates. Excess relative risk functions of breast cancer mortality have been obtained from two different case-control studies exposed to ionizing radiation, with different follow-up time: the Canadian Fluoroscopy Cohort Study (1950–1987) and the Life Span Study (1950–1985 and 1950–1990), whereas relative risk functions for incidence have been obtained from the Life Span Study (1958–1993), the Massachusetts tuberculosis cohorts (1926–1985 and 1970–1985), the New York post-partum mastitis patients (1930–1981) and the Swedish benign breast disease cohort (1958–1987). Relative risks from these cohorts have been transported to the target population undergoing screening in the Valencian Community, a region in Spain with about four and a half million inhabitants. The SCREENRISK software has been developed to estimate radiological detriments in breast screening. Some hypotheses corresponding to different screening conditions have been considered in order to estimate the total risk associated with a woman who takes part in all screening rounds. In the case of the VBCEDP, the total radio-induced risk probability for fatal

breast cancer is in a range between $[5 \times 10^{-6}, 6 \times 10^{-4}]$ versus the natural rate of dying from breast cancer in the Valencian Community which is $9.2 \times 10^{-3}$. The results show that these indicators could be included in quality control tests and could be adequate for making comparisons between several screening programs.

## 1. Introduction

Mammography is used to aid in the diagnosis of breast cancer diseases in women. The aim of routine breast screening is to identify abnormalities as early as possible in the sojourn time interval, the period between breast cancer diagnosis by mammography and detection by physical examination (medical or self-exploration) or by other techniques. The European Protocol on Dosimetry in Mammography (European Commission 1996) is the document that stipulates the regulation for the basic test procedures, dose measurements and their frequencies in breast screening programs, ensuring high-quality mammography and comparison between centres.

Although screening for the early detection of breast diseases reduces breast cancer mortality, it is well known that the diagnosis by mammography presents risks for women undergoing screening (Hammerstein *et al* 1970). Some studies have been devoted to the assessment of health risks and benefits in breast screening, where mean glandular dose ($d_g$) to the breast has been widely accepted as the relevant quantity in mammography (Dance 1990, Law 1997, Law and Faulkner 2001).

The potential number of induced cancers by mammography is a useful risk indicator in a breast screening program. Hazard functions have to be transported from epidemiological studies with a high statistical power, such as the atomic bomb survivors or the patients exposed for medical reasons to high doses (Schneider *et al* 1995), to the population under study. These studies are subjected to many sources of uncertainties and to questionable assumptions in calculations. However, some indicators derived from these studies could be adequate to make comparisons between different breast screening programs, from a qualitative point of view.

In a previous paper, the authors developed the first model to study the radiological detriment associated with the Valencian Breast Cancer Early Detection Program (VBCEDP) using the existent data up to the year 1998 from 11 breast screening centres (León *et al* 2001). In the present paper, the models have been improved, including new photon spectra for the mammography units, and they have been used to obtain radiological risk assessment employing a larger number of screening centres in the Valencian Community.

The presented methodology is based on a parametric approach, through Markov processes, of hazard functions for breast cancer incidence and mortality. Radiological detriment in women undergoing screening mammography has been estimated transporting relative risk functions for fatal breast cancer from two different cohorts, the Life Span Study (LSS) and the Canadian Tuberculosis Cohort Study (CFS) (Howe and Laughlin 1996), employing four models, based on those first developed by the Fifth Committee on the Biological Effects of Ionizing Radiations, the BEIR V Committee (National Research Council 1990), and included later in the UNSCEAR 2000 report (United Nations 2000).

There are a greater number of breast cancer incidence cohorts after radiation exposure, compared with mortality cohorts, and most of these studies derive from medical diagnostics or treatments. A recent paper analyses the incidence of radio-induced breast cancers, studying

eight large case-control studies, including the Hiroshima and Nagasaki cohorts (Preston *et al* 2002). Incidence rates have been transported from four of these case-control studies to the women undergoing screening mammography in the Valencian Community, chosen to include different countries and the higher absorbed mean doses.

This paper is organized in four sections, as follows. The method is focused on the estimation of screen-program-induced breast cancers, as developed in section 2. In section 3, the methodology has been applied to transport risks from the studied cohorts to the women undergoing screening in the Valencian Breast Cancer Early Detection Program (VBCEDP), estimating the radiological assessment assuming different screening hypotheses. Finally, in section 4 the discussion of the results and the conclusions are presented.

## 2. Methodology

### *2.1. Hazard functions and survivorship matrix*

The hazard function $\lambda(t|\vec{z})$ is defined formally as the natural conditional probability of a system failure in the time interval $t$ to $(t + \mathrm{d}t)$, given a set of covariates $\vec{z}$ and assuming that there has been no failure by $t$. Applied to an individual, the discrete hazard function or mortality rate, $\lambda_{\mathrm{all}}(t|\vec{z})$ is defined as the natural probability of dying from any cause at age $t_{k+1}$, given that one is alive at age $t_k$.

The survivorship between one age and the next one behaves as a Markov process, with a Leslie or transition matrix $S(t_k \rightarrow t_{k+1})$. The element $s_{ij}$ of $S(t_k \rightarrow t_{k+1})$ represents the probability that an individual in state $i$ goes to state $j$ between $t_k$ and $t_{k+1}$. In a finite state space, the survivorship matrix $S$ can be expressed as

$$S(t_k \rightarrow t_{k+1}) = \begin{pmatrix} 1 - \lambda_{\mathrm{all}}(t_k) & \lambda_{\mathrm{all}}(t_k) \\ 0 & 1 \end{pmatrix} \tag{1}$$

where state 1 represents being alive and state 2, being dead. As can be seen in (1), $S$ is a non-negative, upper triangular and stochastic matrix. The states of matrix $S$ are defined to fill all the space of events, and to be exclusive and independent, therefore the sum of each row, $\sum_j s_{ij}$, must be equal to 1.

The hazard function for breast cancer mortality in the absence of radiation exposure is called the baseline hazard function and it has been represented as $\lambda_{\mathrm{fbc}}(t_k)$. This function defines the probability of dying from breast cancer at age $t_{k+1}$, being alive at $t_k$. The survivorship transition matrix, considering breast cancer mortality as an independent state, can be represented as

$$S(t_k \rightarrow t_{k+1}) = \begin{pmatrix} 1 - \lambda_{\mathrm{all}}(t_k) & \lambda_{\mathrm{all}}(t_k) - \lambda_{\mathrm{fbc}}(t_k) & \lambda_{\mathrm{fbc}}(t_k) \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

where state 2 represents being dead from any cause, excluding breast cancer, which is estimated in state 3.

The hazard function $\Lambda_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}})$ of an individual exposed to ionizing radiation is defined as the probability of dying from a breast cancer at age $t_{k+1}$, conditioned to the subject's set of covariates $\vec{z}_{\mathrm{fbc}}$. This vector includes all risk factors associated with radio-induced breast cancer, such as attained age (age at death or cancer incidence), age-at-exposure, absorbed dose or sex, and those associated with breast cancer, such as stage at diagnosis, genetic factors or diet. By definition, the hazard function $\Lambda_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}})$ does not differentiate among deaths due to natural breast cancer mortality and due to a radio-induced one. Therefore, another quantity is needed to estimate only the risk of dying from a radio-induced breast cancer.

The excess absolute risk for breast cancer at an age $t_k$, $\mathrm{EAR}_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}})$, is defined as the probability of dying at age $t_{k+1}$ from a radio-induced breast cancer after an exposure to ionizing radiation at age $t_e$. The latency period $L$ is the time delay between exposure and the diagnosis of clinical cancer. It extends from a few years (leukaemia/thyroid cancer in children) to several years (other cancers induced by radiation). It has been assumed that death from a radio-induced breast cancer never occurs suddenly, without a clinical examination, and hence $t_k \geqslant t_e + L$, where $t_e$ is the age-at-exposure. The excess absolute risk is calculated therefore as the difference between the hazard function in the exposed population and the baseline hazard one, as

$$\mathrm{EAR}_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}}) = \begin{cases} \Lambda_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}}) - \lambda_{\mathrm{fbc}}(t_k) \geqslant 0 & \text{if} \quad t_k \geqslant t_e + L \\ 0 & \text{if} \quad t_k < t_e + L \end{cases}.$$

Similarly, the hazard function $\Lambda_{\mathrm{all}}(t_k|\vec{z}_{\mathrm{fbc}})$ is defined as the probability of dying from any cause at age $t_{k+1}$, after an exposure to the ionizing radiation at $t_e$, and it is calculated as

$$\Lambda_{\mathrm{all}}(t_k|\vec{z}_{\mathrm{fbc}}) = \begin{cases} \lambda_{\mathrm{all}}(t_k) + \mathrm{EAR}_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}}) & \text{if} \quad t_k \geqslant t_e + L \\ \lambda_{\mathrm{all}}(t_k) & \text{if} \quad t_k < t_e + L \end{cases}$$

where it has been assumed that the exposure to screening increments only the mortality rate from breast cancer.

The survivorship transition matrix, including radio-induced breast cancer mortality, is represented, for $t_k \geqslant t_e + L$, as

$$S(t_k \to t_{k+1}|\vec{z}_{\mathrm{fbc}}) = \begin{pmatrix} 1 - \Lambda_{\mathrm{all}}(t_k|\vec{z}_{\mathrm{fbc}}) & \lambda_{\mathrm{all}}(t_k) - \lambda_{\mathrm{fbc}}(t_k) & \lambda_{\mathrm{fbc}}(t_k) & \mathrm{EAR}_{\mathrm{fbc}}(t_k|\vec{z}_{\mathrm{fbc}}) \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

where state 3 represents now being dead from breast cancer, excluding deaths due to radio-induced breast cancers, which is estimated in state 4.

### *2.2. Risk of exposure-induced death (REID) and cancer (REIC)*

The probability that a discrete time Markov chain will be in state $n$ at age $t_{k+1}$, after an exposure at age $t_e$, with $t_k \geqslant t_e + L$, has been denoted as $s_n(t_{k+1}|\vec{z}_{\mathrm{fbc}})$, $\vec{s}(t_{k+1}|\vec{z}_{\mathrm{fbc}})$ being the row vector including probabilities of all possible states in the chain. Throughout the discrete time Chapman–Kolmogorov equation, we obtain the relation between the starting vector in the chain, $\vec{s}^0 = \vec{s}(t_e)$, and the current state, $\vec{s}(t_{k+1}|\vec{z}_{\mathrm{fbc}})$, as

$$\vec{s}(t_{k+1}|\vec{z}_{\mathrm{fbc}}) = \vec{s}^0 \prod_{j=e}^{k} S(t_k \to t_{k+1}|\vec{z}_{\mathrm{fbc}}) = \vec{s}^0 S(t_e \to t_{k+1}|\vec{z}_{\mathrm{fbc}}) \tag{2}$$

where $S(t_e \to t_{k+1}|\vec{z}_{\mathrm{fbc}})$ denotes the cumulative survivorship transition matrix of an individual from the age at exposure $t_e$ to the age $t_{k+1}$, and where it has been assumed that the starting vector is $\vec{s}^0 = [1, 0, 0, 0]$, which is the probability of being alive at age-at-exposure $t_e$. Operating (2), we finally reach the cumulative probabilities, defined for $t_k \geqslant t_e$,

$$s_1(t_{k+1}|\vec{z}_{\mathrm{fbc}}) = \prod_{j=e}^{e+L-1} [1 - \lambda_{\mathrm{all}}(t_j)] \prod_{j=e+L}^{k} [1 - \lambda_{\mathrm{all}}(t_j) - \mathrm{EAR}_{\mathrm{fbc}}(t_j|\vec{z}_{\mathrm{fbc}})] \tag{3a}$$

$$s_2(t_{k+1}|\vec{z}_{\mathrm{fbc}}) = \sum_{j=e}^{k} s_1(t_j|\vec{z}_{\mathrm{fbc}})[\lambda_{\mathrm{all}}(t_j) - \lambda_{\mathrm{fbc}}(t_j)] \tag{3b}$$

$$s_3(t_{k+1}|\vec{z}_{\text{fbc}}) = \sum_{j=e}^{k} s_1(t_j|\vec{z}_{\text{fbc}})\lambda_{\text{fbc}}(t_j) \tag{3c}$$

$$s_4(t_{k+1}|\vec{z}_{\text{fbc}}) = \sum_{j=e+L}^{k} s_1(t_j|\vec{z}_{\text{fbc}})\,\text{EAR}_{\text{fbc}}(t_j|\vec{z}_{\text{fbc}}) \tag{3d}$$

where $s_1$ is the probability at $t_{k+1}$ for an individual of being alive, $s_2$ is the probability of dying at $t_{k+1}$ by any kind of cancer excluding breast cancer, $s_3$ is the probability of dying at $t_{k+1}$ because of breast cancer (excluding radio-induced breast cancer) and $s_4$ is the Nelson–Ålen estimator, the probability of dying from a radio-induced breast cancer at $t_{k+1}$, after an exposure to ionizing radiation.

The Markov chain with cumulative transition matrix $S(t_e \rightarrow t_{k+1}|\vec{z}_{\text{fbc}})$ is said to be irreducible if there is a positive integer $n$ such that $s_{ij}^0 > 0$, at the $n$th iteration between $t_e$ and $t_{k+1}$. If a matrix is non-irreducible, there are one or several absorbing states with probability equal to 1, from which the process cannot move to the others. The matrix $S$ is non-irreducible. These absorbing states are death due to all causes, due to breast cancer and due to radio-induced breast cancer.

It has been assumed, without loss of generality, that death always occurs before or at an age $t_M$, that is, the hazard function $\Lambda_{\text{all}}(t_k|\vec{z}_{\text{fbc}})$ is equal to unity before or at $t_M$. Therefore, the element $s_{11} = 0$ at any age after or at $t_M$ and hence (2) reaches a steady state value defined by $\vec{\pi} = \lim_{k\to\infty} \vec{s}(t_{k+1}|\vec{z}_{\text{fbc}}) = \vec{s}(t_M|\vec{z}_{\text{fbc}})$, where $\pi_1 = 0$, corresponding to the probability of being alive at $t_k > t_M$. State 4 in $\vec{\pi}$ gives the probability that a woman dies at any moment of her life from a radio-induced breast cancer after an exposure to ionizing radiation at age $t_e$. The risk of exposure-induced death (REID) is derived from this estimator and it is calculated as

$$\text{REID}\,(t_e|\vec{z}_{\text{fbc}}) = \sum_{j=e+L}^{M} \hat{s}_1(t_j)\text{EAR}_{\text{fbc}}(t_j|\vec{z}_{\text{fbc}}) \tag{4}$$

where $\hat{s}_1(t_j|\vec{z}_{\text{fbc}})$ is the estimator of the survival function, defined in the UNSCEAR 1988 report (United Nations 1988) without modifying by a reduced survival due to radiation, that is $\hat{s}_1(t_k) = \prod_{j=e}^{k}[1 - \lambda_{\text{all}}(t_j)]$.

The risk of exposure-induced cancer (REIC) is defined as the probability that an individual suffers a radio-induced cancer, not necessarily fatal, over all of his or her life. The REIC is estimated through an expression derived from (4), as

$$\text{REIC}\,(t_e|\vec{z}_{\text{in}}) = \sum_{j=e+L}^{M} \hat{s}_1(t_j)\,\text{EAR}_{\text{in}}(t_j|\vec{z}_{\text{in}}) \tag{5}$$

where $\text{EAR}_{\text{in}}$ is the excess absolute risk for breast cancer incidence and $\vec{z}_{\text{in}}$ is the vector of covariates for breast cancer incidence.

### *2.3. Risk transport model for breast cancer incidence and mortality*

Transport models are employed in epidemiology to estimate cancer incidence and mortality rates in a population under study from another population whose rates are known from observation. In a cohort study, a defined population, exposed to ionizing radiation, is followed forwards in time, until censoring or death occurs. The Cox Proportional Hazards (PH) or multiplicative model (Cox 1982) is widely used in many analyses of biomedical and cancer survival data, mainly due to its mathematical simplicity. It assumes that the ratio of the excess

absolute risk and the baseline hazard function both of a given population is constant and equal to the excess relative risk of any cohort $m$. We have considered an extension of the Cox PH model to estimate excess absolute risks, as $\mathrm{EAR}^{(m)}(t_k|\vec{z}^{(m)}) = \lambda(t_k)[ERR(\vec{z}^{(m)})]$, $t_k \geqslant t_e + L$, where $\mathrm{ERR}^{(m)}$ is the excess relative risk of the cohort $m$ for breast cancer. It can be seen how the excess risk of the cohort $m$ is transported to the population with baseline hazard function $\lambda(t_k)$, both for incidence and mortality.

### *2.4. Excess relative risk for incidence and mortality*

The excess relative risk (ERR) is a parameter used to transport risks between populations which have been exposed to radiation and have different baseline rates. The risk assessment from one population is used to estimate effects that would be seen in other populations with a low statistical power, that is, with a low probability of being observable.

The Radiation Effects Research Foundation Life Span Study (LSS) and the Canadian Fluoroscopy Cohort Study (CFS) are the two major series of breast cancer mortality studies, due to exposures to high and acute doses of low LET, and fractionated doses of ionizing radiation, respectively. The Fifth Committee on the Biological Effects of Ionizing Radiations of the National Research Council, the BEIR V Committee (National Research Council 1990), developed the first model for breast cancer mortality based on the Hiroshima and Nagasaki survivors between 1950 and 1980, including the follow-up in the Canadian Fluoroscopy study (Miller *et al* 1989) between 1950 and 1980. In a later study, the follow-up was extended another seven years in the Canadian cohort and another five years in the atomic bomb survivors (Howe and Laughlin 1996). Recently, the UNSCEAR 2000 report (United Nations 2000) has published new findings from an extended follow-up of breast cancer incidence and mortality among the Japanese atomic bomb survivors (1950–1990) (Pierce *et al* 1996).

For this reason, four different models of breast cancer mortality have been chosen to estimate risks in the Valencian Breast Cancer Early Detection Program: (1a) the Canadian Fluoroscopy Cohort Study (1950–1987), which excludes the Nova Scotia subcohort for uncertainties in dosimetry; (2a) the Life Span Study cohort, which includes only the female atomic bomb survivors between 1950 and 1985; (3a) the LSS with follow-up until 1990, depending on age-at-exposure; and (4a) depending on attained age. Although other studies estimate the mortality excess due to the treatment of benign diseases, such as ankylosing spondylitis (Weis *et al* 1994), or to the diagnostic examinations of scoliosis patients (Doody *et al* 2000), the CFS and the LSS are the two major series of breast cancer mortality. These models have been chosen to include the latest available follow-up of series of breast cancer mortality arising from radiation exposures, with different baseline hazard functions (Asian and North American).

Case-control studies for incidence breast cancer after radiation exposure are more numerous than the mortality ones. A recent study is focused on these cohorts (Preston *et al* 2002), including those analysed in the UNSCEAR 2000 report. We have chosen four of these studies to transport risks to the women undergoing screening, those which include different countries and the higher absorbed mean doses: (1b) the Life Span Study for incidence breast cancer (1958–1993); (2b) the Massachusetts fluoroscopy study, for tuberculosis patients (TBO) and the extension (TBX) (Boice *et al* 1991); (3b) the New York acute post-partum mastitis cohort (APM) (Shore *et al* 1986); and (4b) the benign breast disease treatment in Sweden (BBD) (Mattson *et al* 1993).

The excess relative risk could be fitted to a general model that includes dependence with both age-at-exposure and attained age at 50 years old. According to the cohort and model $m$,

**Table 1.** Parameters for the estimation of excess relative risk (ERR) (mortality and incidence).

| | Cohort | $t^{(m)}$ | $\alpha^{(m)}$ ($Gy^{-1}$) | $\beta^{(m)}$ | $\gamma^{(m)}$ | Percentage change per decade increase in age-at-exposure (%) |
|---|---|---|---|---|---|---|
| Mortality | CFS[a]<br>1950–1987<br>Age-at-exposure | 25 | 0.16<br>[0.053, 0.30][d] | 0 | −0.10<br>[−0.16, −0.043] | Not included[e] |
| | LSS[a]<br>1950–1985<br>Age-at-exposure | 25 | 0.94<br>[0.11, 2.03] | 0 | −0.044<br>[−0.20, 0.029] | Not included |
| | LSS[b]<br>1950–1990<br>Age-at-exposure | 30 | 1.34<br>Not included | 0 | Not included | −32<br>Not included |
| | LSS[b]<br>1950–1990<br>Attained age | – | 2.35<br>Not included | 1.5<br>Not included | 0 | 0 |
| Incidence | LSS[c]<br>1958–1993<br>Attained age | – | 2.10<br>[1.6, 2.8] | −2.0<br>[−2.8, −1.1] | 0 | Not included |
| | TBO/TBX[c]<br>Attained age | – | 0.74<br>[0.4, 1.2] | −2.0<br>[−2.8, −1.1] | 0 | Not included |
| | APM[c]<br>All ages | | 0.56<br>[0.3, 0.9] | 0 | 0 | Not included |
| | BBD[c]<br>Age-at-exposure | 25 | 1.9<br>[1.3, 2.8] | 0 | Not included | −60<br>[−71, 44] |

[a] Source: Howe and Laughlin (1996).
[b] Source: UNSCEAR 2000 report.
[c] Source: Preston *et al* (2002).
[d] 95% confidence intervals.
[e] 'Not included' means that the quantity is not provided in the reference.

the ERR is fitted with

$$\mathrm{ERR}(\vec{z}^{(m)}) = \alpha^{(m)}\theta(s)\Phi(d_g)\exp(\gamma^{(m)}(t_e - t^{(m)})\left(\frac{t_k}{50}\right)^{\beta^{(m)}} \tag{6}$$

where $\Phi(d_g)$ is the dose response with dose $d_g$ to the breast, $s$ is the gender of the individual and $\theta(s)$ is a function that depends on gender and cancer type, equal to unity for breast cancer on female. The covariate vector for the ERR is the same for incidence and mortality, and it includes the variables $\vec{z} = [t_k, t_e, d_g, s]$. Table 1 summarizes the chosen cohorts, models and their references, published by Howe and Laughlin (1996), Preston *et al* (2002) and in the UNSCEAR 2000 report (United Nations 2000).

The ICRP (1991) recommends that a dose and dose-rate effectiveness factor (DDREF) should be included in risk estimates at low doses and low dose-rates. There is some discussion about what DDREF is necessary to apply for estimating radiological risk assessment in mammography. A DDREF = 2 is employed in the NRPB (1993) for breast cancer during screening, whereas a DDREF = 1 is used by the US Environmental Protection Agency (1994). Due to that the multiplicative model is linear with the ERR, risks derived from different

**Table 2.** Average values of voltage, tube loading, compressed breast thickness and mean glandular dose per film and per sample population.

| | Number of women | Tube voltage (kV) | Tube loading (mAs) | Compressed breast thickness (cm) | $d_g$ (mSv) |
|---|---|---|---|---|---|
| 1st (2001) | 1861 | $27 \pm 2$ | $102 \pm 51$ | $5.3 \pm 1.3$ | $1.46 \pm 0.62$ |
| 2nd (2002) | 1772 | $28 \pm 2$ | $93 \pm 46$ | $5.6 \pm 1.3$ | $1.29 \pm 0.53$ |
| 3rd (2003) | 1980 | $28 \pm 2$ | $82 \pm 42$ | $5.5 \pm 1.3$ | $1.23 \pm 0.47$ |

DDREF will be proportional to this factor. Hence, it has been assumed a DDREF $= 1$, which corresponds with the maximum risk estimates.

## 3. Application to the estimation of the radiological detriment in the Valencian Breast Cancer Early Detection Program (VBCEDP)

### *3.1. Introduction*

In 1992 the Valencian Breast Cancer Early Detection Program (VBCEDP) started in the Valencian Community, a region of Spain with approximately four and a half million inhabitants. Up to now, 24 mammography units are installed in public hospitals and health centres, all over the region.

### *3.2. Sample populations and quality control parameters*

A first sample population of one hundred radiographed women from each screening centre in operation was extracted between October and November of 2001, immediately after quality control testing. Two more sample populations were extracted between October and November of 2002 and 2003, immediately after quality control testing. For each examination, tube voltage (kV), filtration, anode material, compressed breast thickness, tube loading (mAs) and the woman's age were recorded. A dependence of glandularity for each woman's breast on compressed breast thickness and age-at-exposure has been assumed (Dance *et al* 2000).

The method to estimate the relevant dose ($d_g$) to the breast is described in detail in the European Protocol on Dosimetry in Mammography (European Commission 1996). The mean glandular dose is derived from measurements of the half value layer (HVL) and the entrance surface air kerma (ESAK), throughout tabulated conversion factors (Dance 1990, Dance *et al* 2000). The mean glandular dose to the breast per exposure has been therefore estimated as $d_g = g\,\mathrm{ESAK}$, where $g$ is a conversion factor, depending on HVL, filtration and anode materials, compressed breast thickness and glandularity. However, in this paper, we have obtained the mean glandular dose through simulations with a different Monte Carlo transport code, MCNP4c2 (Briesmeister 2000), and with a different library of x-ray photon spectra. The x-ray tube spectra have been obtained from the Catalogue of Diagnostic X-Ray Spectra and other Data© (IPEM 1988), for a range of voltages of 25 (0.34 mm Al) to 31 kV (0.39 mm Al), with a molybdenum (Mo) anode, and a 0.03 mm molybdenum (Mo)/1 mm beryllium (Be) filter. A comparison has been made between tabulated and calculated conversion factors, showing slight differences (Ramos *et al* 2003).

Table 2 summarizes the number of women per sample population, the average values and the standard deviation of the tube voltage, tube loading, compressed breast thickness and mean glandular dose per film of the three sample populations.

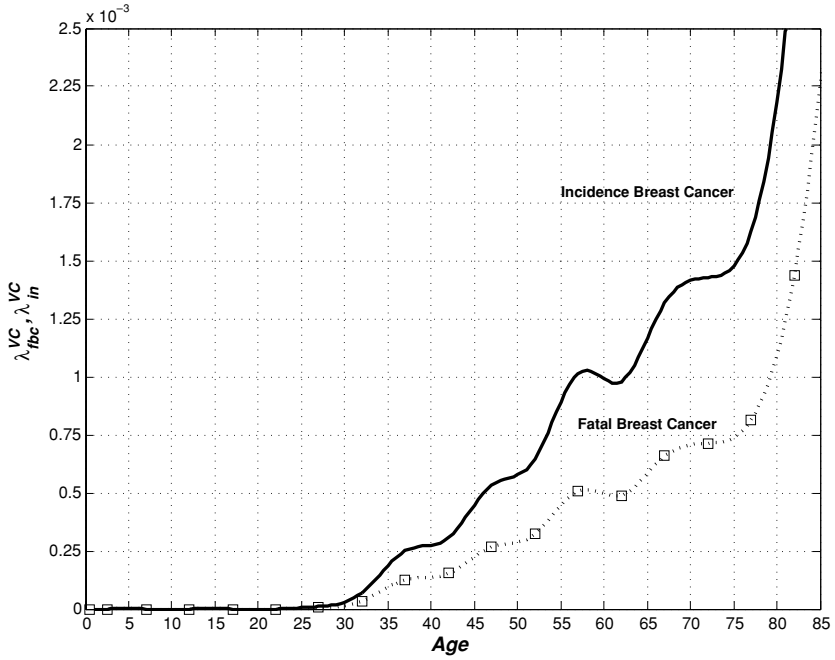



**Figure 1.** Baseline hazard functions for breast cancer incidence and mortality in the Valencian Community (2000).

### *3.3. Baseline hazard functions and latency period in the VBCEDP*

In Spain, mortality rates are generally published by the National Statistics Institute (http://www.ine.es) with at least a four-year delay, divided into five-year age groups, until a maximum age group of 85 years old. We have assumed that observations are centred in the middle age of each age group interval. On the other hand, there is no public registered data concerning the breast cancer incidence rate, extended to the whole Valencian Community. In a similar region in Spain (Navarra Community) a follow-up of breast cancer incidence and mortality was made in the 1993–97 period, showing that mortality is approximately a third lower than incidence (Ardanaz *et al* 2001). The incidence rate has been estimated through the mortality hazard function and the lethality fraction ($f$) for breast cancer published and proposed by the NCRP (1993), based on a previous ICRP publication (1991). Although the introduction of screening and the improvements in treatment could have decreased the lethality of breast cancer, the maximum risk estimates would correspond with the lethality fraction proposed in the NCRP (1993). Therefore, the incidence rate has been calculated as $\lambda_{\mathrm{in}}^{\mathrm{VC}} = \lambda_{\mathrm{fbc}}^{\mathrm{VC}}(t_k) \big/ f(t_k)$.

Although several explanatory mortality models have been proved to fit the baseline hazard functions in the Valencian Community (Gompertz, Makeham, Perks, Beard and Weibull) (Yashin *et al* 2000), the lack of data and the difficulty in finding a good estimator have driven us to propose a purely descriptive model, based on cubic spline interpolation, to fit the mortality data. Figure 1 shows the evolution with age of the baseline hazard functions $\lambda_{\mathrm{in}}^{\mathrm{VC}}$ and $\lambda_{\mathrm{fbc}}^{\mathrm{VC}}$ in the year 2000, where the experimental values (□) have been fitted with a cubic spline interpolation.

The breast cancer risks have been transported to the population undergoing screening, assuming that the baseline hazard functions related on the exposed population in the VBCEDP

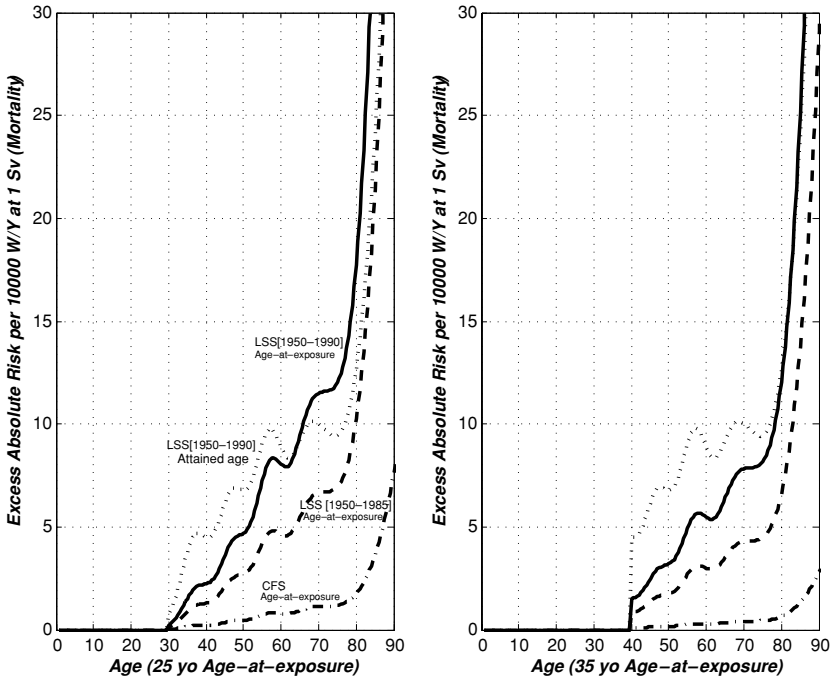



**Figure 2.** Excess absolute risk for fatal breast cancer per 10 000 women-year at 1 Sv (DDREF = 1) in the Valencian Community at 25 and 35 years old age-at-exposure and 5 years latency period, transporting risks from the CFS (— · —), LSS with follow-up 1950–1985 (– – –), and LSS with follow-up (1950–1990), based on an age-at-exposure model (——) and attained age model (· · · · · ·).

are equal to those derived from the whole Valencian Community (VC) population, that is $\lambda^{\mathrm{VBCEDP}}(t_k) = \lambda^{\mathrm{VC}}(t_k)\,\forall t_k$, where $\lambda(t_k)$ is the hazard function for breast cancer incidence or for mortality.

The latency period is not an easy quantity to determine in the estimation of the excess absolute risk. In the UNSCEAR 1988 report (United Nations 1988) the minimum latency period used for the risk projection was 10 years for all cancers, derived from the observation of the atomic bombs survivors (20–24 years for breast cancer) (NCRP 1993). For the LSS, there are few observations of risk increasing for the 10 years after exposure. However, the follow-up for the Canadian Fluoroscopy Study started in 1950, whereas the great majority of exposures occurred in the 1930s and 1940s. In the CFS cohort, the 5 year after first exposure were excluded, corresponding to a minimum latency period of 5 years. Therefore a 5 year latency period for both incidence and mortality has been chosen, which is a conservative value, to estimate risks in the VBCEDP, in the absence of more information.

Figures 2 and 3 illustrate the EAR per 10 000 women-year-sievert resulting after an exposure at two different ages, 25 and 35 years old, both with a latency period $L = 5$ years, for the different studied cohorts, and transported to the Valencian Community population. As it can be seen for mortality, the highest values are due to the LSS cohort with follow-up 1950–1990, being higher for the attained age model at lower ages, whereas the lowest ones derive from the CFS. In the case of breast cancer incidence, the higher values at 25 years old age-at-exposure are due to the results derived from the Swedish patients. However, these risks are reduced considerably when the age-at-exposure increases, with the Life Span Study being the cohort with the highest risks at higher ages-at-exposure.

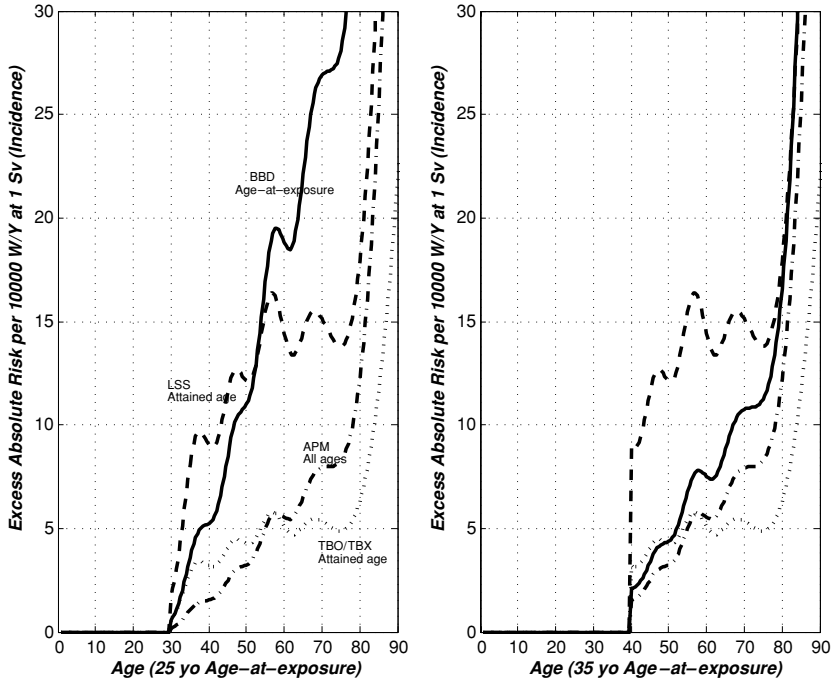
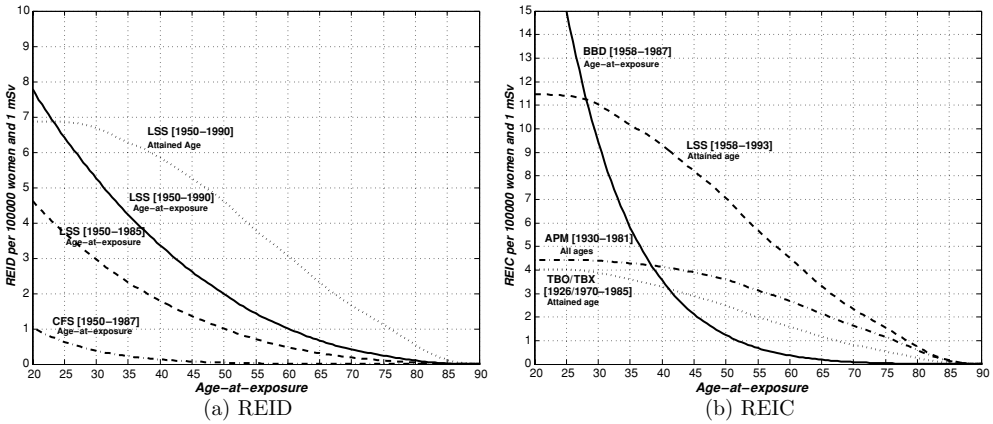



**Figure 3.** Excess absolute risk for incidence of breast cancer per 10 000 women-year at 1 Sv (DDREF = 1) in the Valencian Community at 25 and 35 years old age-at-exposure and 5 years latency period, transporting risks from the LSS (– – –), the TBO/TBX (· · · · · ·), the APM (— · —) and the BBD cohorts (——).




(a) REID (b) REIC

**Figure 4.** Risk of exposure-induced death (REID) and cancer (REIC) at different age-at-exposure per 100 000 women at 1 mSv in the Valencian Community (DDREF = 1).

The risk of exposure-induced death, REID$(t_e|d_g)$, and the risk of exposure-induced cancer, REIC$(t_e|d_g)$, defined before, are the individual cumulative probability that a woman dies or suffers, respectively, from a radio-induced breast cancer in any moment of her life after an exposure to ionizing radiation with relevant dose $d_g$. Figures 4(a) and (b) present the REID and REIC estimators per 100 000 women at 1 mSv in the Valencian Community.

### *3.4. The SCREENRISK software: simulation and implementation*

The VBCEDP is directed towards asymptomatic women between 45 and 69 years old, with an initial age lower than other screening programs. The screening examination consists of two exposures per breast, craniocaudal (CC) and mediolateral oblique view (OBL), the first time that the woman participates in the program (first round) and for the age group between 45 and 46 years old, and a single mammogram (OBL) per breast in subsequent rounds. The screening rounds are spaced every two years and two independent radiologists read each mammogram.

In a breast screening program, women are invited to undergo mammography between an initial age ($a$) and a final age ($b$), with a constant screen interval ($s$), and receiving normally one exposure per breast at each time. There are different indicators when evaluating the associated cancer risk during breast screening. These indicators are adequate to make comparisons between several programs, and they could be included in the quality control of each screening centre. The average radiological risk ($A$) for breast cancer incidence and mortality, in a given instant of the screening, can be estimated as

$$A_{\mathrm{fbc}} = \sum_{j=a}^{\mathrm{b}} v(t_j)\,\mathrm{REID}^{(m)}(t_j|d_{g\,j})w(t_j) \tag{7a}$$

$$A_{\mathrm{in}} = \sum_{j=a}^{\mathrm{b}} v(t_j)\,\mathrm{REIC}^{(m)}(t_j|d_{g\,j})w(t_j) \tag{7b}$$

where $v(t_j)$ is the number of views per breast in each visit, $w(t_j)$ is the fraction of population and $d_{g\,j}$ is the average mean glandular dose per film at an age-at-exposure $t_j$. Table 3 shows the average radiological risk in the VBCEDP per sample population. The highest values are obtained for the Life Span Study and the attained age model, for the Canadian Fluoroscopy Cohort being practicably negligible. The mortality risk derived from the last 5 years follow-up of the atomic bomb survivors, included in the UNSCEAR 2000 report, is approximately double that from the 1950–1985 follow-up, for the same model (age-at-exposure) and four times for the attained age model.

Another estimator ($B$) is the cumulative risk probabilities associated with a woman who takes part in all screening rounds in her life, and they can be estimated as

$$B_{\mathrm{fbc}} = \sum_{k=1}^{N} v(t_{j(k)})\,\mathrm{REID}^{(m)}(t_{j(k)}|d_{g\,j(k)})r(t_{j(k)}) \tag{8a}$$

$$B_{\mathrm{in}} = \sum_{k=1}^{N} v(t_{j(k)})\,\mathrm{REIC}^{(m)}(t_{j(k)}|d_{g\,j(k)})r(t_{j(k)}) \tag{8b}$$

where $N = (b-a)/s+1$ is the maximum number of times that a woman could visit a screening centre during the program and $j(k) = a+s(k-1)$ is the age when the exposure takes place. The $r(t_{j(k)})$ is the reliability survival function, defined as $r(t_{j(k)}) = \hat{s}_1(t_{j(k)})/\hat{s}_1(t_{j(1)})$ and corrects (8$a$) and (8$b$), taking into account the possible natural death during the breast screening. These estimators determine the total cumulative probability that a woman undergoing screening mammography would develop a radio-induced breast cancer, and they are directly comparable with the natural probability of breast cancer mortality.

From these equations we have developed the SCREENRISK software, based on Matlab© 6.5, which estimates the risk of exposure-induced cancer (REIC) and fatal cancer (REID) for a specific cancer in a given population. The program has been implemented on a PC Pentium© IV CPU 1.70 GHz, 896 MB RAM and Windows XP OS.

**Table 3.** Average radiological risk for breast cancer incidence and mortality per $10^5$ women and year in the VBCEDP.

| | Cohort | VBCEDP | |
|---|---|---|---|
| Mortality | CFS | 1st (2001) | $0.05 \pm 0.02$ |
| | (1950–1987) | 2nd (2002) | $0.04 \pm 0.02$ |
| | Age-at-exposure | 3rd (2003) | $0.04 \pm 0.01$ |
| | LSS | 1st (2001) | $1.21 \pm 0.52$ |
| | (1950–1985) | 2nd (2002) | $1.04 \pm 0.44$ |
| | Age-at-exposure | 3rd (2003) | $1.02 \pm 0.39$ |
| | LSS | 1st (2001) | $2.43 \pm 1.03$ |
| | (1950–1990) | 2nd (2002) | $2.08 \pm 0.87$ |
| | Age-at-exposure | 3rd (2003) | $2.03 \pm 0.78$ |
| | LSS | 1st (2001) | $5.96 \pm 2.53$ |
| | (1950–1990) | 2nd (2002) | $5.14 \pm 2.15$ |
| | Attained age | 3rd (2003) | $4.99 \pm 1.92$ |
| Incidence | LSS | 1st (2001) | $8.98 \pm 3.83$ |
| | (1958–1993) | 2nd (2002) | $7.76 \pm 3.24$ |
| | Attained age | 3rd (2003) | $7.55 \pm 2.90$ |
| | TBO/TBX | 1st (2001) | $3.17 \pm 1.35$ |
| | (1926/1970–1985) | 2nd (2002) | $2.73 \pm 1.14$ |
| | Attained age | 3rd (2003) | $2.66 \pm 1.02$ |
| | APM | 1st (2001) | $4.81 \pm 2.05$ |
| | (1930–1981) | 2nd (2002) | $4.17 \pm 1.73$ |
| | All ages | 3rd (2003) | $4.05 \pm 1.55$ |
| | BBD | 1st (2001) | $1.46 \pm 0.62$ |
| | (1958–1987) | 2nd (2002) | $1.22 \pm 0.53$ |
| | Age-at-exposure | 3rd (2003) | $1.21 \pm 0.47$ |

Some hypotheses have been considered to compare the total radio-induced risk probability under the VBCEDP screening conditions and under other situations:

Hypothesis 1: $a = 45$; $b = 69$; $s = 2$; $N = 13$, $v(45–46) = 2$; $v(47–69) = 1$.

Hypothesis 2: $a = 50$; $b = 69$; $s = 2$; $N = 10$, $v(50–69) = 2$.

Hypothesis 3: $a = 50$; $b = 69$; $s = 1$; $N = 20$, $v(50–69) = 2$.

Hypothesis 4: $a = 50$; $b = 69$; $s = 1$; $N = 20$, $v(50–69) = 1$.

Hypothesis 1 (H1) corresponds to the screening conditions in the VBCEDP; Hypothesis 2 (H2) corresponds to the Galician Breast Cancer Early Detection Program, another national screening program; Hypothesis 3 (H3) corresponds to some breast screening programs in USA and Hypothesis 4 (H4) is accomplished in other screening programs.

Tables 5 and 4 present the results obtained for incidence and mortality risk probabilities, respectively. For the calculations with the SCREENRISK software, the average glandular doses corresponding to the third sample population for each hypothesis have been taken.

## 4. Discussion and conclusions

Since there are still few studies concerning breast cancer mortality derived from radiation exposures, risk estimates transported from these cohorts are subjected to many sources of

**Table 4.** Total radio-induced risk probabilities for breast cancer mortality per $10^{-4}$ associated with a woman who takes part in all screening rounds in her life.

| | Model | H1 | H2 | H3 | H4 |
|---|---|---|---|---|---|
| CFS | Age-at-exposure | $0.05 \pm 0.02$ | $0.04 \pm 0.01$ | $0.07 \pm 0.02$ | $0.03 \pm 0.01$ |
| LSS (1950–1985) | Age-at-exposure | $1.20 \pm 0.47$ | $1.33 \pm 0.49$ | $2.50 \pm 0.92$ | $1.25 \pm 0.46$ |
| LSS (1950–1990) | Age-at-exposure | $2.40 \pm 0.94$ | $2.74 \pm 1.05$ | $5.13 \pm 1.89$ | $2.56 \pm 0.94$ |
| LSS (1950–1990) | Attained age | $5.87 \pm 2.28$ | $7.63 \pm 2.80$ | $14.38 \pm 5.30$ | $7.19 \pm 2.65$ |

**Table 5.** Total radio-induced risk probabilities for breast cancer incidence per $10^{-4}$ associated with a woman who takes part in all screening rounds in her life.

| | Model | H1 | H2 | H3 | H4 |
|---|---|---|---|---|---|
| LSS | Attained age | $8.88 \pm 3.45$ | $11.32 \pm 4.16$ | $21.32 \pm 7.86$ | $10.66 \pm 3.93$ |
| TBO/TBX | Attained age | $3.13 \pm 1.21$ | $3.99 \pm 1.46$ | $7.51 \pm 2.77$ | $3.75 \pm 1.38$ |
| APM | All ages | $4.75 \pm 1.83$ | $6.47 \pm 2.38$ | $12.22 \pm 4.50$ | $6.11 \pm 2.25$ |
| BBD | Age-at-exposure | $1.44 \pm 0.57$ | $1.25 \pm 0.45$ | $2.32 \pm 0.85$ | $1.16 \pm 0.42$ |

uncertainties. It is important to highlight that only one of the mortality models derives from an epidemiological study of patients exposed in medical applications, the Canadian Fluoroscopy Study. This cohort could be more adequate to transport risks than the Life Span Study, because it provides more information on effects of gradual low-dose-rate exposures, as applied in mammography. Further, risks derived from this cohort are the lowest of all, comparing both incidence and mortality detriments. However, the Canadian Fluoroscopy Cohort presents different dose responses between sanatorium centres, which could indicate errors or uncertainties in dosimetry, as occurs in the Nova Scotia subcohort, and for this reason, this subcohort was excluded (Howe and Laughlin 1996). However, other subcohorts of this study could be subjected to the same uncertainties in dosimetry.

The average radiological detriment, measured as the total number of screen-induced breast cancers, is lower than $9 \times 10^{-5}$ women-year for all the incidence cohorts and models and lower than $6 \times 10^{-5}$ in the case of fatal cancers. The values agree with the results presented in a previous paper by the authors (León *et al* 2001). The differences between the radiological detriments from the Canadian Fluoroscopy Study and those derived from the Life Span Study are considerable. Comparisons among the Canadian and the Life Span Study cohorts are susceptible to some differences, such as the background rates of breast cancer mortality in Canada and Japan (much lower in the latter), the approaches to estimating dose or the mean age of the exposure. Furthermore, in the Life Span Study, the possible contribution of neutrons in the case of the Hiroshima subcohort and effects of thermal or mechanical injury could influence risk models, concluding that it is necessary to perform more studies and increase the follow-up to estimate mortality due to a radio-induced breast cancer. As compared above, differences between the results from the age-at-exposure and the attained age model are considerable for the Life Span Study.

Regarding the total risk, a 45 year old Valencian woman has a natural risk probability of developing a fatal breast cancer of about $9.2 \times 10^{-3}$ in the period from 45 to 69 years old while the total risk associated with radiation in the screening program is in a range between $[5 \times 10^{-6}, 6 \times 10^{-4}]$, approximately, depending on the cohort and model (H1). Hypotheses 2 and 4 are slightly higher than that followed in the VBCEDP (H1), with the lowest average detriments, except for the CFS cohort. This is due to the double number of views taken between 50 and 69 years old (H2) and the annual screening interval (H4). As can be seen, the

highest values correspond to hypothesis 3, when the program starts at 50 years old and a double view is taken every year. The high values obtained under hypothesis 3, which correspond to some screening conditions in North America, make necessary a study of the detection rates and screening procedures, revealing the necessity of new epidemiological studies to better adjust the ERR and EAR for breast cancer incidence and mortality.

Comparing the results for all hypotheses, the conditions in the Valencian Breast Cancer Early Detection Program provide the lowest detriments, although the values are comparable to those obtained with hypotheses 2 and 4, with a double projection (H2) and an annual screening interval (H4). This is because the contribution of the 45–50 years old age group is quite important.

In terms of radiological risk, the screening proceedings in the Valencian Community are acceptable, but these values should be compared with detection rates in order to find the optimal program. In all cases and models, the risk induction rate is very low, compared with the detected breast cancer rate in the VBCEDP, which is approximately $3 \times 10^{-3}$ screened woman, during the period 2001–2003, verifying that the screening is acceptable in terms of radiological risks. Nevertheless, to make a full comparison, we would need to know the detection rates associated with other hypotheses.

As a conclusion, hazard functions for radio-induced cancers are subjected to many uncertainties, for instance, the risk transport model, the DDREF, the latency period, the lethality fraction or the vector of covariates used to fit the relative risks from the case-control studies. Despite all uncertainties, the average radiological detriment and the total radio-induced risk probabilities for radio-induced breast cancer are good qualitative indicators in a breast screening program to make comparisons among mammography units or programs, or between different time instants of the same program.

## Acknowledgments

This work is funded with the project 4.3 of the European Breast Cancer Network and by the MCYT (Spain). We are also grateful to the Valencian Breast Cancer Early Detection Program (VBCEDP).

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