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ProZES – a tool for assessment of assigned share of radiation in probability of cancer development

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ProZES

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Disclaimer

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Contents

1. INTRODUCTION

1.1. Occupational exposure and radiation-induced cancer

Wide use of radiation and radioactivity in medicine, industry, science, and military applications leads to inevitable occupational exposures of personnel involved. Existing radiation protection limits for occupational exposure are set up to prevent deterministic effects of radiation and minimize potential harm of radiation due to stochastic effects (ICRP 2007). Stochastic effects include cancers and hereditary effects. Cancer is a common disease and development of cancer might result from either occupational exposure or other cause not related to radiation exposure. Correspondingly, any decision on a compensation claim should investigate causal links between occupational exposure and observed disease.

Various implementations of compensation schemes have been developed in Argentina, France, Japan (for A-bomb survivors), Russia, UK, and US (ILO, 2010). In Germany, decision-making on compensation in the case of cancer after occupational radiation exposure is made using radiation-epidemiological tables (Chmelevsky et al. 1995), which neither reflect current state of knowledge on radiation-induced carcinogenesis nor account for inherent uncertainties of risk estimates and probability of cancer causation. Thus, existing tables need to be upgraded and replaced with modern, flexible approach, capable to account for details of personal occupational radiation exposure history as well as existing uncertainties in epidemiological data and models used to express risk of radiation exposure.

1.2. Basic terms

The Incidence rate, defined as the number of new cases of a certain disease in the observed population per year, is a common epidemiological measure of risk (see e.g. Estève et al. 1994). The incidence rate observed in the general population not affected by the risk factor of interest is commonly called baseline incidence rate, λ_0, while additional disease cases that appear as an effect of the risk factor are considered as excess incidence rate, h. Excess risk due to the risk factor is expressed either as excess absolute risk (EAR), i.e. as additional incidence rate due to effect of the risk factor, $EAR = h$, or as excess relative risk (ERR) expressing additional incidence rate in terms of the baseline one: $ERR = h/\lambda_0$.

Probability of causation (BEIR, 2006) or assigned share of radiation exposure in probability of cancer development can be expressed in terms of *ERR*:

$$Z = \frac{ERR}{1 + ERR} \tag{1.1}$$

or in terms of *EAR*:

$$Z = \frac{EAR}{EAR + \lambda_0} \tag{1.2}$$

1.3. Estimates of risk of radiation-induced cancer

As follows from Eqs. **Error! Reference source not found.** and **Error! Reference source not found.**, probability of cancer causation can be expressed via excess relative or excess absolute risks. The most widely used source of epidemiological information for assessment of risk of radiation-induced pathologies (mostly cancers) is an epidemiological cohort of people who survived A-bombing in Hiroshima and Nagasaki, the so-called Life Span Study (LSS) cohort. Of the four types of cancer considered in the present report: stomach, colon, lung and female breast cancer, the first three are derived from the LSS epidemiological data. This cohort, albeit the most significant source of information on effects of radiation to human health, is not the only source of epidemiological information. For example, the risk model for female breast cancer presented here is based on results of a combined (pooled) study of several cohorts, including but not restricting to the LSS cohort.

The lung cancer model presented in this report is based on recent analysis of the LSS cohort data by Furukawa et al. (2010). However, this model does not account for effects of exposure to radon and its daughters. Extension of the lung cancer model to include effects of radon exposure will be impossible without consideration of other studies, like study of uranium miners' cohort (see e.g. Leuraud et al. 2011).

Cancer incidence in the LSS cohort is available only since 1958. Also, members of the LSS cohort had been affected by single acute external mixed photon and neutron exposure. Assessment of radiation-induced risk after prolonged exposure, low dose rate exposures, exposures to different radiation types or within 13 years after exposure may require to look for other sources of pertinent epidemiological information. Among possible sources of such information might be: Chernobyl-related studies of thyroid cancer, Mayak and Techa River cohorts of people exposed occupationally or environmentally due to acute and prolonged releases of radioactive wastes.

1.4. ProZES — development for Germany

As a basis and prototype for the German program, the U.S. program IREP (Kocher et al. 2008) has been selected. However, a decision has been made not to simply copy methodology, approaches, and software tools which are used by IREP. Instead, it was decided to base development of the German program on critical review and re-analysis of existing methodologies, models, and their parameters, on intensive discussions and approval of those by leading national and world experts in the field.

This report summarizes the results of this analysis and describes the methodology which has been developed for implementation in the program ProZES — Programm zur Berechnung der Zusammenhangswahrscheinlichkeit einer Erkrankung und einer Strahlenexposition.

2. EMPIRICAL MODELS OF CANCER RISK

2.1. General description of empirically-based models of cancer risk

Empirically-based models of radiation-induced cancer risk relate the excess incidence rate to radiation dose and other adjusting factors. Depending on the type of disease, suggested functional dependence on the dose may differ. The most common and widely used are linear and linear-quadratic shapes. Other important factors that are used to adjust risk are: attained age *a*, age at exposure *e*, gender *s*, and other parameters specific to the study population.

Alternative to empirical models are mechanistic models of carcinogenesis. Although the latter may demonstrate significant advantages compared to empirical models, mechanistic modelling needs radiobiological information which is extensively gathered during last decades but still is not always sufficient or accurate enough to build or to validate models of cancer development. Therefore, as advised by SSK, current work is based on empirical models derived from well-established epidemiological studies.

2.2. MECAN models for LSS cohort

Epidemiological data for the LSS cohort (Preston et al., 2007) have been fitted using the MECAN program (Kaiser, 2010). The LSS incidence data for the follow-up period 1958–1998[1] encompass survivors from various population groups or strata. These strata are commonly differentiated according to:

- city of residence: Hiroshima or Nagasaki;
- presence in either city at the time of detonation (characterized by distance from the hypocentre);
- participation in screening programs during the follow-up period via Adult Health Study (AHS).

Correspondingly, baseline incidence rate depends not only on specific cancer cite, gender, and age-group but also on combination of strata-specific correction factors. On the other hand, functions describing cancer risk are selected in the form independent on strata-specific factors. That is, a set of fit parameters includes: radiation dose d, parameters common to the cohort and target population $C = \{a, e, \dots\}$, and parameters specific to the cohort only $S = \{city, NIC, AHS, \dots\}$. Then, models for ERR and EAR depend only on d and C:

$$ERR(d, C) \text{ and } EAR(d, C),$$

while the baseline function does not depend on dose and can be factorized into two parts depending on either common or cohort-specific parameters:

$$\lambda_0(C, S) = \lambda_{0,fit}(C)\, b(S). \tag{2.1}$$

The factorisation (2.1) allows representing the model baseline as:

[1] The data used for fitting cancer risk models can be found on web page of Radiation Effects Research Foundation in Hiroshima: http://www.rerf.jp/library/dl_e/lssinc07.html

$$\lambda_{0,LSS}(C) = \lambda_{0,fit}(C)\overline{b} \tag{2.2}$$

where $\overline{b}$ is approximately equal to the average strata-specific correction factor:

$$\overline{b} = \frac{\sum_S b(S)PY(C,S)}{\sum_S PY(C,S)}, \tag{2.3}$$

where $PY(C,S)$ is the number of person-years in a strata defined by parameter groups *C* and *S*.

An expression used to model the fit baseline has the following general form:

$$\begin{aligned}\lambda_{0,fit} = \quad & \exp\left[\beta_0 + \beta_1 \ln\frac{a}{a_c} + \beta_2 \ln^2\frac{a}{a_c} + \beta_3 \max^2\left(0, \ln\frac{a}{\beta_4}\right) + \right. \\ & \left. + \beta_5 \max^2\left(0, \ln\frac{a}{\beta_6}\right) + \beta_7(e-e_c) + \beta_8(e-e_c)^2\right],\end{aligned} \tag{2.4}$$

where age 'calibration' parameters a_c and e_c are commonly taken equal to fixed values of 70 and 30 years, correspondingly. Parameters β_4 and β_6 (so-called 'spline joints') in MECAN can be treated as fit parameters unlike fixed values traditionally used by other models (BEIR 2006, Preston 2002, Land et al. 2003).

Cohort-specific correction factor for the baseline is modelled as:

$$b(S) = \exp\left((city-1)\,\beta_{city} + NIC\,\beta_{NIC} + ahs\,\beta_{ahs} + \cdots\right) \tag{2.5}$$

where parameter *city* equals to 1 for the cohort members from Hiroshima and to 2 for members from Nagasaki. As it follows from Eqs. (2.1) and (2.4), the fit baseline $\lambda_{0,fit}$ is simply a baseline for the cohort members from Hiroshima (*city*=1), who were in the city at the time of bombing (*NIC*=0) and who were not involved in Adult Health Study (*ahs*=0).

Expressions used to fit ERR and EAR are functionally equivalent and look as follows:

$$\left.\begin{matrix}ERR\\EAR\end{matrix}\right\} = (\alpha_0 d + \alpha_1 d^2)\exp\left(\alpha_2 d - \alpha_3(e-e_c) - \alpha_4(e-e_c)^2 + \alpha_5 \ln\frac{a}{a_c} + \alpha_6 \ln^2\frac{a}{a_c} + \alpha_7 s\right) \tag{2.6}$$

where *d* is radiation dose and the sign of *s* denotes gender:

$$s = \begin{cases} +1, \text{ females} \\ -1, \text{ males} \end{cases}$$

3. MODEL SELECTION AND MULTI-MODEL INFERENCE

Selection of the best model is based on multi-model inference (MMI) approach. According to this approach, the possible plausible models are ranked according to a value of the Akaike information criterion (AIC):

$$AIC = dev + 2K, \tag{3.1}$$

where $dev = -2\ln(L(\beta|x, g))$ is the deviance computed from log-likelihood given the data x, the model g and the vector β of parameter estimates; K is the number of the model parameters. The AIC serves as a penalized measure of lack of model fit, i.e. the less the *AIC* value is, the better the given model describes the data. Detailed information on this subject can be found elsewhere (see e.g., Burnham and Anderson 2002, Claeskens and Hjort 2008, Anderson 2008).

Considered models can be arranged according to their AIC values and the difference of AIC between the best model (minimum AIC) and others:

$$\Delta AIC_i = AIC_i - \min(AIC) \tag{3.2}$$

Then, weight for a model i is expressed as follows:

$$\omega_i = \frac{\exp\left(-\frac{1}{2}\Delta AIC_i\right)}{\sum_j \exp\left(-\frac{1}{2}\Delta AIC_j\right)}. \tag{3.3}$$

In ProZES, MMI is used to construct a distribution of ERR and, correspondingly, assigned share Z estimates. The weights (3.3) are used to randomly decide within the main sampling loop, which model should be selected to calculate a risk value for distribution in a specific cycle. That is, the i^{th} model contributes $N\omega_i$values to the total sample of size N.

4. CANCER RISK MODIFYING FACTORS

4.1. Uncertainties in dosimetry for members of LSS cohort

In IREP (Kocher et al. 2008), stochastic correction factors are applied to cancer risk estimates in order to account for uncertainties in dosimetry data for members of the LSS cohort. The suggested set of correction factors corresponds to DS86 dosimetry system (Roesch 1987). Currently, the dosimetry system DS02 (Young and Kerr 2005) is in use. Uncertainties related to dosimetry of atomic bomb survivors had been revised by Pierce et al. (2008) who accounted for both new results in the DS02 system and modern views on interaction of classical and Berkson errors.

To analyse the additional uncertainty of LSS risk estimates due to shared uncertainties in the dosimetry system might require substantial efforts and time. On the other hand, one can expect (based on the results of Pierce et al., 2008, also) that this additional uncertainty will have a small impact on the uncertainty distribution of the risk estimates. As long no systematic study of the impact of shared uncertainties has been conducted, a multiplicative factor with a lognormal probability density function centred at 1.0 with a GSD=1.1 will be used as a default approach:

$$F_d \sim LN(\mu = 0; \sigma = \ln(1.1)) \tag{4.1}$$

Additional uncertainty comes out of peculiarities of neutron dosimetry for the LSS cohort members. Some recent publications (Kellerer et al., 2006; Rühm and Walsh, 2007; Sasaki et al., 2008) have shown neutron RBE varying among the cohort members depending on their distance from hypocentre. Contrary to commonly used value of RBE=10, Rühm and Walsh (2007) suggested higher values – about 20 or higher.

Fitting for LSS cohort with various neutron RBE values resulted in varying ERR estimates (Kaiser, 2011). These estimates scaled by the ERR value for RBE=10 are shown in Fig. 4.1.

Based on judgment of members of the UNSCEAR and SSK expert groups[2], neutron RBE values are assumed to have triangular probability distribution in the range from 5 to 30 with mode 10. This distribution can be translated to a distribution of ERR values using the scaled approximations shown in Fig. 4.1. That is, assuming scaled ERR for breast as representative for external organs and average of scaled ERRs for colon and stomach as representative for internal organs, one can propagate the assumed distribution of neutron RBE to obtain risk correction factors for various types of organs. The resulting distributions representing additional uncertainty of ERR due to uncertainties of neutron contribution to total absorbed doses for LSS cohort members are shown in Fig. 4.2. Main statistics of the distributions are given in Table 4.1. These distributions are used to sample a stochastic correction factor F_{n-RBE}, which represents uncertainty of LSS dosimetry due to variations of neutron RBE.

[2] During period 2010–2012, these experts were: O. Hoffman, P. Jacob, J. Kiefer, C. Land, D. Preston.

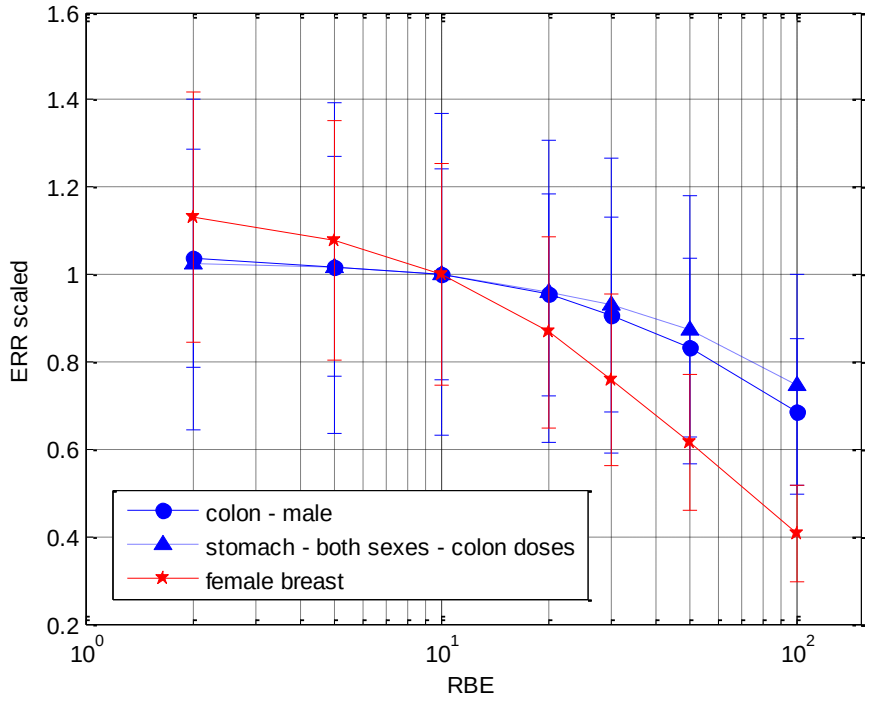

Fig. 4.1 Scaled ERR for colon, stomach, and breast cancers fitted for the LSS cohort with various neutron RBE values.

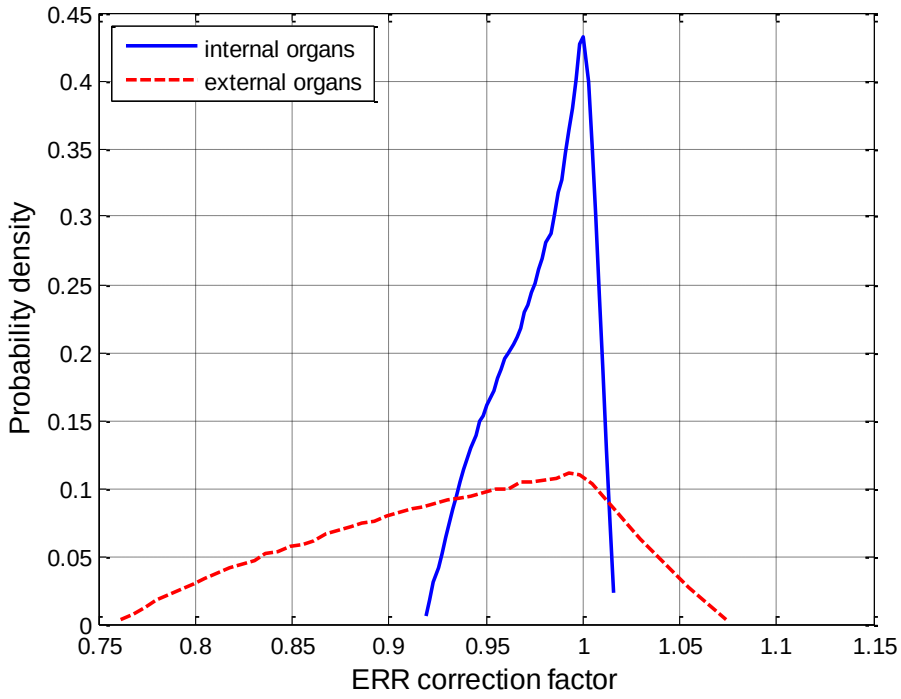

Fig. 4.2 Probability density functions for ERR correction factors for external and internal organs accounting for uncertainty in LSS dosimetry related to neutron RBE (triangle distribution T(5,10,30) assumed).

Table 4.1. Main statistics of ERR stochastic correction factors accounting for uncertainties in neutron dosimetry for LSS cohort

Organs	min	Percentile (%)									max
		1	5	10	25	50	75	90	95	99	
Internal	0.926	0.926	0.937	0.945	0.962	0.983	0.998	1.005	1.008	1.013	1.013
External	0.781	0.781	0.810	0.833	0.883	0.942	0.991	1.021	1.037	1.058	1.059

4.2. Period of latent cancer development

Functions accounting for latency period in cancer development, adopted and implemented in IREP, have been found to result in unrealistically large latency periods; therefore, the main developer of IREP program, SENES (Oak Ridge, US), was asked to review the existing approach and to suggest a set of new parameters or a new function to account for the latency period.

In April 2012, SENES suggested the new (so-called 'asymmetric') shape for the latency function:

$$F_L = \frac{1}{1 + \exp\left(-\frac{\ln t - \ln t_0}{\tau}\right)} \tag{4.2}$$

where parameters *u* and *s* are defined as follows:

- for all solid cancers: $t_0 \sim U(3,4)$ and $\tau = 0.16$;
- for leukaemia: $t_0 \sim U(1.25,1.75)$ and $\tau = 0.1305$.

Resulting curves are shown in Fig. 4.3, where solid lines correspond to mean values of the parameter t_0, while dashed lines represent latency curves for minimum and maximum values of t_0.

The latency function (4.2) can be re-written as:

$$F_L = \frac{1}{1 + \left(\frac{t_0}{t}\right)^{\eta}} \tag{4.3}$$

where $\eta = 1/\tau$. The latter expression albeit being mathematically equivalent to Eq. (4.2) is more efficient in computations (ca. 20–50% depending on hardware and selected optimization level), so it has been implemented in ProZES.

In ProZES, the correction factor to account for latency effects is treated as individual-specific, i.e. strictly correlated for different exposures.

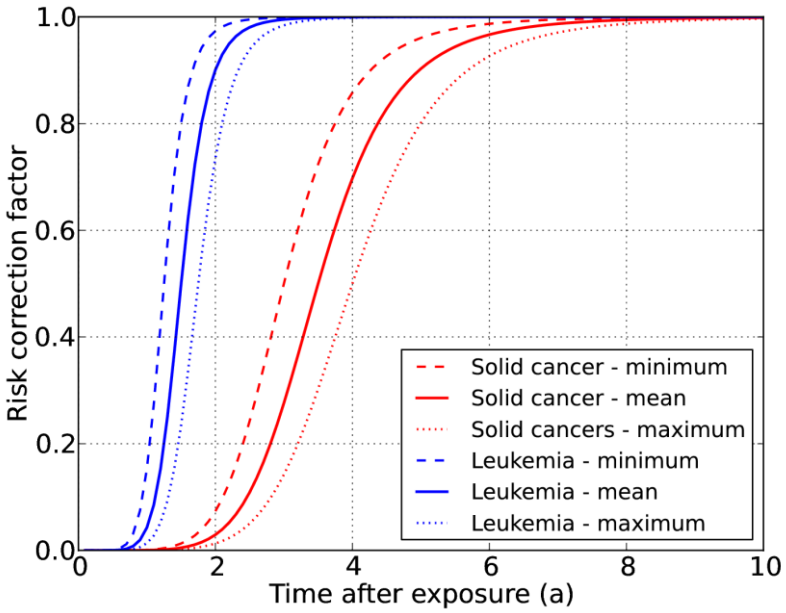

Fig. 4.3 Functions for risk correction factor to account for latency time of cancer.

4.3. Low dose rate exposure

In the IREP program (Kocher et al., 2008), a discrete distribution for the dose and dose-rate effect factor (DDREF) is used. The BEIR Committee suggested a continuous distribution for this factor (BEIR, 2006). Additionally, Jacob et al. (2009) reviewed outcomes of several epidemiological studies for people occupationally exposed and showed that the results of the studies do not suggest risk reduction for low dose-rate occupational conditions. All these representations are shown in Fig. 4.4.

For implementation in ProZES, it is suggested:

- to consider dose-rate effects, only; therefore, not the traditional term DDREF but a term DREF (dose-rate effect factor) is used here;
- to model the DREF by a log-normal distribution with geometric mean GM and geometric standard deviation GSD, with the latter parameter depending on dose rate (mGy h^{-1});
- to assume both parameters to be 1.0 at the upper border of the range of low-dose rates: 0.1 mGy min^{-1} = 6 mGy h^{-1} (UNSCEAR 2000, ICRP 2005);
- to assume values of both parameters for dose rates that are typical for higher occupational dose rates (taken as 1 mGy d^{-1}≈0.042 mGy h^{-1}) to correspond to results of Jacob et al. (2009), *i.e.* GM=1.0 and GSD=1.5.

In this approach, GM is assumed to be identical to 1.0, and GSD is assumed to depend logarithmically on dose rate (Fig. 4.5) resulting in:

$$GSD(\dot{d}) = \begin{cases} 1.1803 - 0.2317 \log_{10}(\dot{d}) & \text{for } \dot{d} \le 6\ \text{mGyh}^{-1} \\ 1 & \text{otherwise} \end{cases} \quad (4.4)$$

Distributions of DREF resulting from the Eq. (4.4) for dose rates 0.001, 0.042, 1, and 5 mGy h^{-1} are shown in Fig. 4.6.

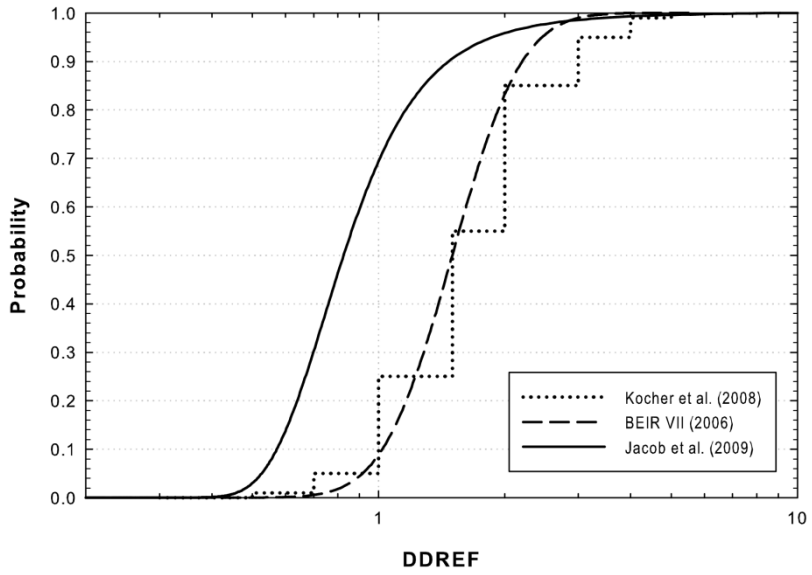

Fig. 4.4 Comparison of DDREF models: Kocher et al. (2008) – dotted step line, BEIR (2006) – dashed line, and Jacob et al. (2009) – solid line

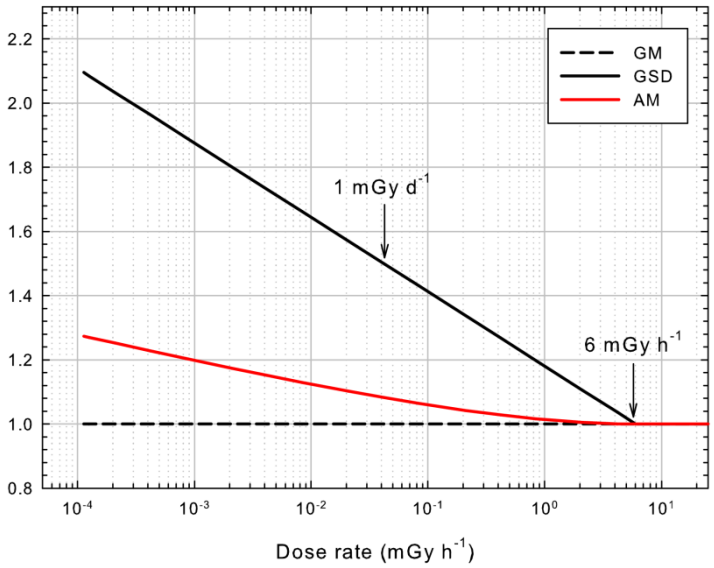

Fig. 4.5 Geometric mean (black solid line) and geometric standard deviation (black dashed line) of DREF and corresponding arithmetic mean (red solid line)

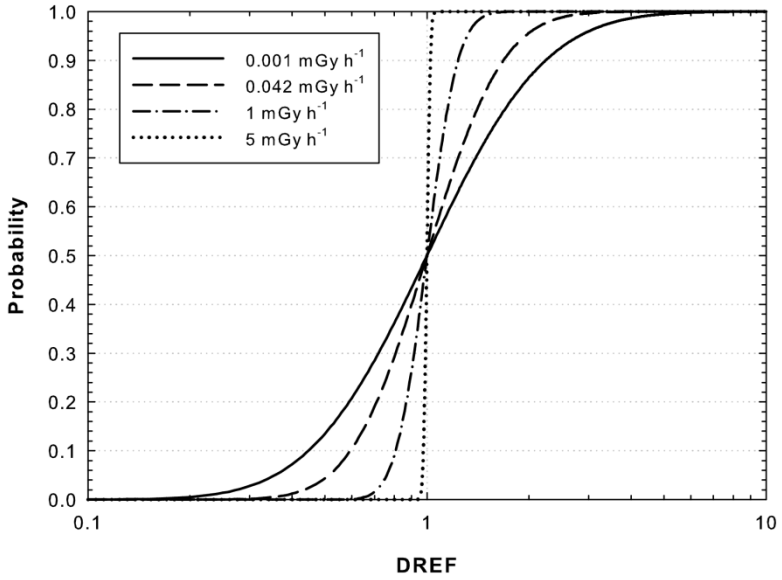

Fig. 4.6 DREF models suggested for ProZES evaluated for various values of dose rate

Table 4.2 Parameters of lognormal distribution of DREF. Knot values are highlighted by bold font

$\dot{d}$ (mGy h^{-1})	GM	GSD	AM
0.0001	1.0	2.107	1.278
0.0002	1.0	2.037	1.253
0.0005	1.0	1.945	1.221
0.001	1.0	1.875	1.198
0.002	1.0	1.806	1.175
0.005	1.0	1.713	1.145
0.01	1.0	1.644	1.123
0.02	1.0	1.574	1.103
0.042	**1.0**	**1.5**	1.082
0.05	1.0	1.482	1.077
0.1	1.0	1.412	1.060
0.2	1.0	1.342	1.043
0.5	1.0	1.250	1.025
1	1.0	1.180	1.014
2	1.0	1.111	1.006
5	1.0	1.018	1.000
6	**1.0**	**1.0**	1.0
10	1.0	1.0	1.0

In ProZES, the DREF correction factor is considered as individual-specific one, i.e. it considered strictly correlated for different exposures.

4.4. Radiation weighting factors

Person-specific occupational radiation exposure can be created by radiation of various types. Various radiation types are known to vary in ability to produce radiobiological effects (damage) to living tissues. Such ability is commonly expressed using concepts of 'radiation quality' or relative biological effectiveness (RBE) of a specific radiation type.

The first version of the ProZES program does not accounts for effects of ionizing radiations with higher lineal energy transfer (LET), like neutrons, heavy charge particles, or even low energy photons or electrons. That is, all calculations of assigned shares correspond to exposures to standard, low-LET radiation, for example high-energy photons ($E_\gamma \geq 250\text{keV}$).

Implementation of RBE correction factors is planned for the second phase of ProZES development. RBE will be considered as individual-specific, i.e. the factor is treated as strictly correlated for different exposures.

5. TRANSFER OF RADIATION RISK TO TARGET POPULATION

Estimates of cancer risk obtained for the studied population in the epidemiological cohort need to be applied to the population in the country of interest (target population). Two possible mechanisms of risk transfer are additive and multiplicative.

The additive transfer mechanism means that excess absolute risk per dose for the target population, EAR_T, is the same as for the studied cohort, EAR_C:

$$EAR_T = EAR_C \tag{5.1}$$

and, correspondingly, excess relative risk for the target population is

$$ERR_T = \frac{EAR_C}{\lambda_{0,T}} \tag{5.2}$$

where $\lambda_{0,T}$ is the baseline incidence rate in the target population.

The multiplicative transfer mechanism assumes that excess relative risk per dose for the target population, ERR_T, is the same as for the studied cohort, ERR_C:

$$ERR_T = ERR_C \tag{5.3}$$

Based on modern notions of carcinogenesis (see e.g. BEIR, 2006), it is assumed that the additive transfer mechanism is more related to radiation impact to so-called starters, i.e. biological processes that result in transition of normal cells to modified, non-stable state. Radiation impact to the modified cells, so-called promoters, may result in their transformation to malignant cells. This transformation process is more likely to be expressed by multiplicative mode of cancer risk transfer. Since ionizing radiation affects both starters and promoters (which may already exist at the time of exposure) at the same time, both additive and multiplicative transfer mechanisms can contribute to risk estimates for the target population. That is, excess relative risk can be represented as a weighted sum of risk estimates according to both mechanisms:

$$ERR_T = (1-f)ERR_C + f\frac{EAR_C}{\lambda_{0,T}} = ERR_C\left(1 - f + f\frac{\lambda_{0,C}}{\lambda_{0,T}}\right) \tag{5.4}$$

where $\lambda_{0,C}$ stands for baseline in the epidemiological cohort, and the coefficient f reflects relative weight of the additive transfer. Thus, the value f=1 corresponds to pure additive transfer mechanism, while f=0 represents pure multiplicative one.

BEIR (2006) suggested mixed transfer mechanism with weighting on logarithmic scale:

$$ERR_T = ERR_C\left(\frac{\lambda_{0,C}}{\lambda_{0,T}}\right)^f \tag{5.5}$$

where f=0.3 is used for all cancer sites other than breast, thyroid, and lung. For lung cancer, BEIR (2006) suggested opposite: f=0.7.

Situations when nothing or little is known about specific transfer mechanism can be addressed by applying uncertain mixing coefficient f. This is an approach utilized by the IREP program (Kocher et al., 2008), namely, probability density distribution of the coefficient f is selected having trapezoidal shape (see Fig. 5.1):

$$p(f) = \frac{10}{11}\begin{cases} 10f + 1 & \text{for } -0.1 < f < 0 \\ 1 & \text{for } 0 \le f \le 1 \\ 11 - 10f & \text{for } 1 < f < 1.1 \end{cases} \tag{5.6}$$

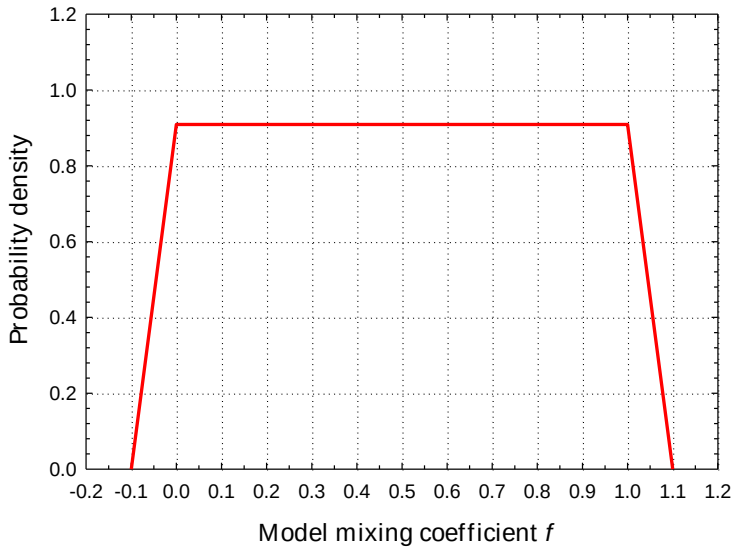

Fig. 5.1 Probability density distribution for random mixing coefficient *f* (Kocher et al., 2008)

Provisionally, the trapezoidal distribution (5.6) is also used in ProZES for modelling of relative risk transfer for colon and stomach cancer. The final form of p.d.f. for the factor *f* is under discussion and may be changed later.

It is important to note that, as it follows from Eq.(5.4), strongly different baselines in the cohort and in the target population result in widening of distribution of excess relative risk for the target population. Such differences in baseline incidence can be originated not only from national peculiarities (like e.g. in case of stomach cancer in Japan and European countries, see Sect. 6.2), but also can be due to the time-dependent differences of baselines in the cohort and in the target population.

Fig. 5.2 illustrates a situation when a case of cancer is observed in the target population in 2006 after radiation exposure in 1976, i.e. 30 years after the exposure. This case in the target population corresponds to a case in the LSS epidemiological cohort being observed in 1975, i.e. 30 years after the nuclear explosion in 1945. This means that for this case the additive term in Eq. (4.4) reads as follows:

$$ERR_C f \frac{\lambda_{0,LSS}(1975)}{\lambda_{0,T}(2006)}, \tag{5.7}$$

thus incorporating not only national but also time-dependent differences between the two baselines.

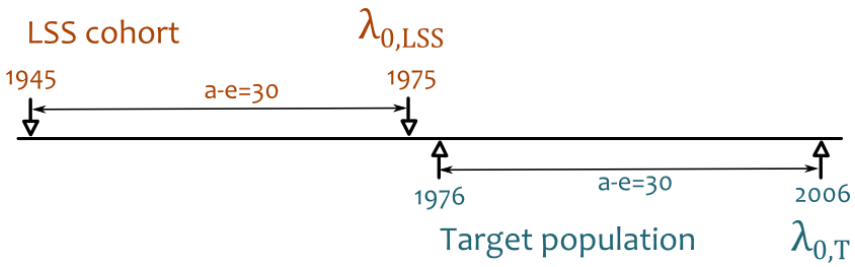

Fig. 5.2 Illustration of time-dependent differences of baselines in an epidemiological cohort (orange) and in the target population (blue) for the same time after exposure

Examples of the baselines for the LSS cohort and for target population in Germany are given in the following sections, where specific cancer types are considered (see e.g. Fig. 6.1 and Fig. 6.2 in Chapter 6).

In practice of assessments, there might be situations when baseline in an epidemiological cohort is not defined. For example, the breast cancer model adopted for ProZES had been derived from a pooled study of several cohorts and is represented via the EAR model (see Chapter 9 for details). In such situations, transfer of cancer risk to a target population misses uncertainty of baselines' ratio. For implementation in ProZES the following solution has been suggested.

It follows from Eq. (5.4) that the stochastic transfer factor can be represented as follows:

$$F(f,x) = 1 - f + fx \tag{5.8}$$

where $x = \lambda_{0,C}/\lambda_{0,T}$ is the ratio of baseline incidence rates in the epidemiological cohort and in the target population. Variability of the factor can be expressed via a normalized factor:

$$F^*(f,x) = \frac{F(f,x)}{\overline{F}}, \tag{5.9}$$

where $\overline{F} = (1+x)/2$ is the average value of the transfer factor (5.8) for the given baseline ratio *x*, thus the variability factor (5.9) is

$$F^*(f,x) = 2\frac{1-f+fx}{1+x}. \tag{5.10}$$

Assume that distribution of the weighting parameter *f* is uniform: $f \sim U(0,1)$. Correspondingly, if baselines in the cohort and in the target population are equal and $x = 1$, then the normalized factor equals to one as well without any variability. On the other hand, if the baselines are different, then $\lim_{x\to\infty} F^*(f,x) = 2f$ and $\lim_{x\to 0} F^*(f,x) = 2(1-f)$, so the normalized factor F^* describing variability of the transfer factor is bounded between 0 and 2, and for known fixed value of *x* is uniformly distributed from $2/(1+x)$ to $2x/(1+x)$.

If the ratio of baselines is unknown (see e.g. sections on breast and lung cancers), then this lack of knowledge can be expressed assuming *x* to be a random variable with a distribution implied by '*a priori'* knowledge (if any).

6. STOMACH CANCER (ICD10:C16)

6.1. Model description

Stomach cancer risk model implemented in ProZES is based on results of fit of the LSS cohort data using MECAN software (Kaiser, 2010). Equations for baseline and risk models are the same as described above (see Eqs.(2.3)–(2.5)). In the case of stomach cancer the difference in baselines in the two cities has been found statistically significant, although not large – weighted baseline differs from the fitted one not more than 4%.

Similar to colon cancer models, the model selection has been done using both minimum AIC and likelihood ratio test (LRT) criteria. Unlike colon cancer models, it was found that gender-dependent models for stomach cancer behave worse than models with common age-dependence for both genders. Thus, 'winners' have been defined among ERR and EAR models with common gender-independent dependence on attained age and age at exposure. The models and their parameters are summarized in Table 6.1.

Table 6.1. Characteristics of the stomach cancer models selected for ProZES using multi-model inference procedure.

Model	No. of cases		K	AIC	Weight
	baseline	excess			
EAR(d, a, a^2)	4577.4	125.6	16	4688.3	0.4277
EAR(d, a)	4570.8	132.2	15	4688.6	0.3581
ERR(d, s, a)	4571.6	131.4	16	4690.1	0.1741
ERR(d, s, e)	4576.6	126.4	16	4693.0	0.0402

6.2. Baseline

Baseline models are gender-dependent but for both genders are described by the same equation:

$$\lambda_{0,fit} = \exp\left(\beta_0 + \beta_1 \ln\frac{a}{70} + \beta_2 \ln^2\frac{a}{70} + \beta_3 \max^2\left(0, \ln\frac{a}{\beta_4}\right) + \beta_7(e-30)\right). \quad (6.1)$$

As described above in Sect. 2.2, the baseline in the whole LSS cohort is represented as weighted average of baselines in various strata. For stomach cancer, the only significant strata parameter is city of residence, therefore:

$$\lambda_{0,LSS} = \lambda_{0,fit}\frac{PY_H + P\,Y_N \exp(\beta_{city})}{PY_H + PY_N}, \quad (6.2)$$

where PY_H and PY_N are person-years accumulated in Hiroshima and Nagasaki sub-cohorts, respectively. For males, PY_H=731077 and PY_N=306213. For females, PY_H=1232155 and PY_N=488748.

Parameters of the baseline (6.1)-(6.2) are given in Table 6.2.

Table 6.2. Gender-dependent parameters of the baseline functions for stomach cancer models.

Model	Parameter						
	β_0	β_1	β_2	β_3	β_4	β_7	β_{city}*
Male							
EAR(d, a, a^2)	−5.023	4.639	−0.242	−10.46	65.4	3.5×10^{-3}	−0.150
EAR(d, a)	−5.028	4.580	−0.313	−10.49	65.6	3.5×10^{-3}	−0.149
ERR(d, s, a)	−5.040	4.487	−0.413	−10.28	65.9	3.4×10^{-3}	−0.141
ERR(d, s, e)	−5.042	4.478	−0.365	−10.30	65.8	3.9×10^{-3}	−0.142
Female							
EAR(d, a, a^2)	−6.194	3.349	0.477	−8.78	71.8	1.40×10^{-2}	same as for males
EAR(d, a)	−6.197	3.267	0.354	–8.50	71.9	1.40×10^{-2}	
ERR(d, s, a)	−6.199	3.231	0.234	−8.32	72.3	1.36×10^{-2}	
ERR(d, s, e)	−6.209	3.187	0.348	−8.49	72.2	1.48×10^{-2}	

* see Eq. (6.2)

Baseline incidence rates observed in various years in the LSS cohort and in the target population may differ strongly, thus increasing uncertainty of risk transfer estimates. Stomach cancer incidence rates in the LSS and in Germany differ strongly as it can be seen in Fig. 6.1 and Fig. 6.2.

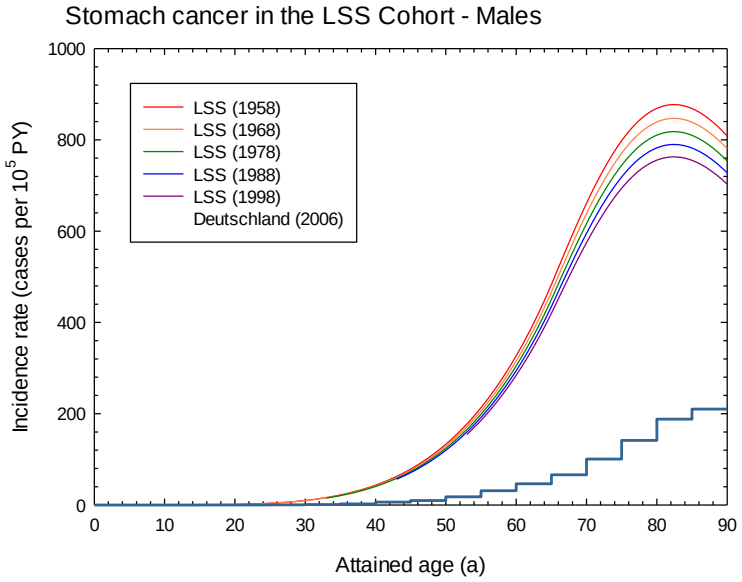

Fig. 6.1 Fitted baseline incidence of male stomach cancer in the LSS cohort for different times after exposure in comparison with stomach baseline incidence among males in Germany in 2006.

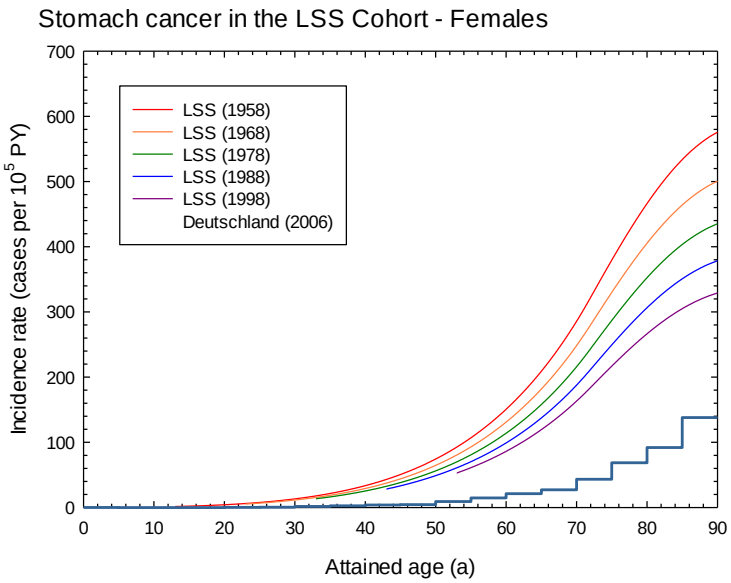

Fig. 6.2 Fitted baseline incidence of female stomach cancer in the LSS cohort for different times after exposure in comparison with stomach baseline incidence among females in Germany in 2006.

Ratio of baselines in the LSS cohort and in the target population (Germany) are high, thus resulting in wider distribution of ERR and, consequently, of assigned share.

6.3. Excess risk

The models selected for ProZES can be explicitly written as follows:

$$EAR(d,a,a^2) = 7.64 \times 10^{-4}\, d \exp\left(-0.584 \ln\frac{a}{70} - 2.796 \ln^2\frac{a}{70}\right) \tag{6.3}$$

$$EAR(d,a) = 9.15 \times 10^{-4}\, d \exp\left(1.992 \ln\frac{a}{70}\right) \tag{6.4}$$

$$ERR(d,s,a) = 0.268\, d \exp\left(-1.818 \ln\frac{a}{70} + 0.545\, s\right) \tag{6.5}$$

$$ERR(d,s,e) = 0.322\, d \exp(-0.031(e-30) + 0.562\, s). \tag{6.6}$$

Of the four selected models, only ERR models are gender-dependent.

The resulting model selected for application in ProZES and its component models are shown in Fig. 6.3–Fig. 6.6.

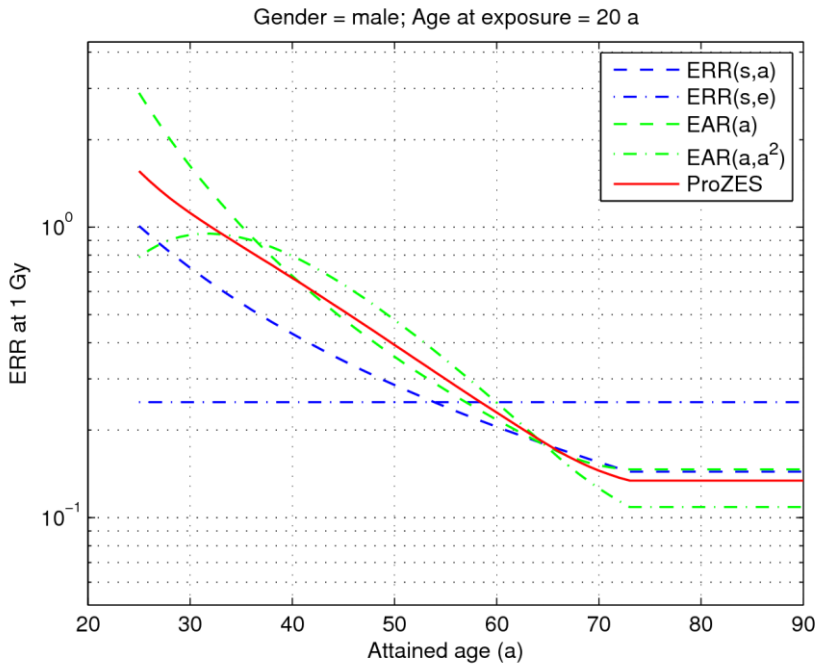

Fig. 6.3 Models for the excess relative stomach cancer risk among males exposed at age 20. Dashed, dot-dashed lines represent component models, red solid line shows a combined model built using multi-model inference.

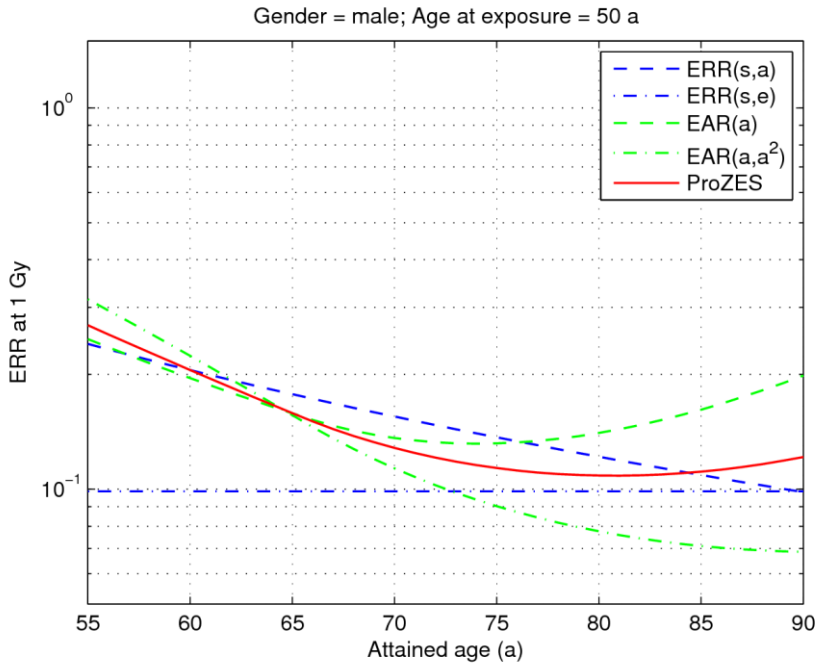

Fig. 6.4 Models for the excess relative stomach cancer risk among males exposed at age 50. Dashed, dot-dashed lines represent component models, red solid line shows a combined model built using multi-model inference.

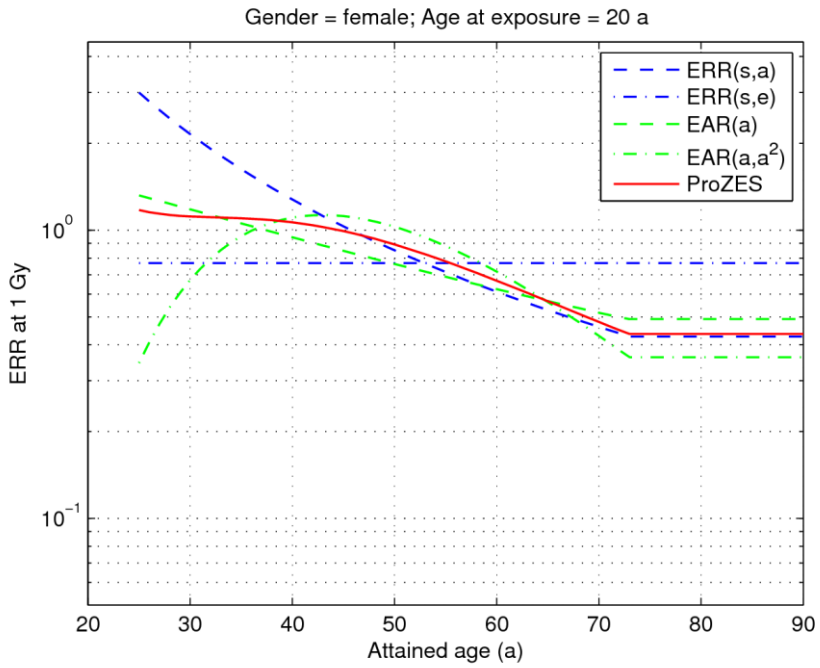

Fig. 6.5 Models for the excess relative stomach cancer risk among females exposed at age 20. Dashed, dot-dashed lines represent component models, red solid line shows a combined model built using multi-model inference.

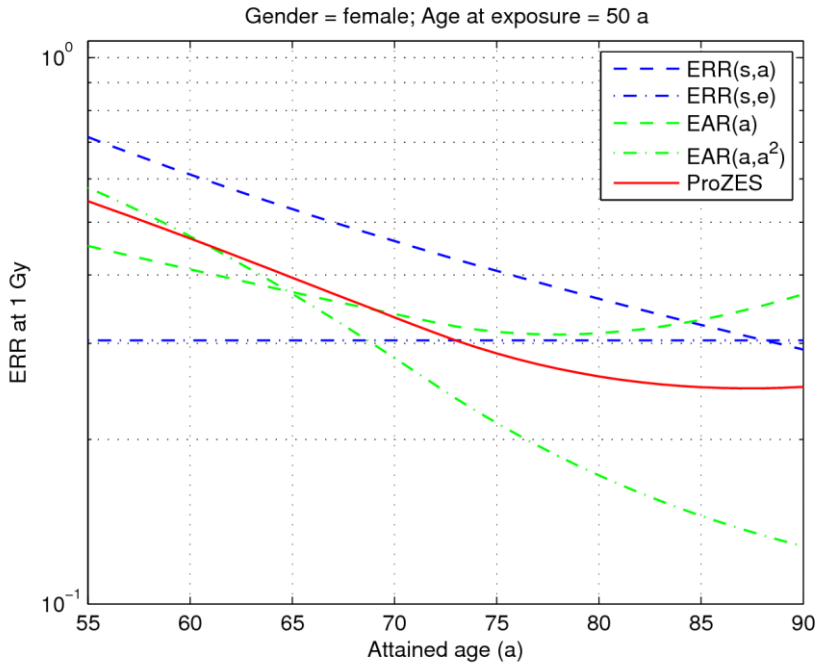

Fig. 6.6 Models for the excess relative stomach cancer risk among females exposed at age 50. Dashed, dot-dashed lines represent component models, red solid line shows a combined model built using multi-model inference.

6.4. Comparison with other approaches

Models implemented in IREP (Land et al., 2003) differ for males and females. For females, the IREP models are:

$$ERR(d,a,e) = 0.449d \exp\left[-0.0472 \min(\max(-15; e-30)) - 1.781 \max\left(0; \ln\frac{a}{50}\right)\right] \quad (6.7)$$

while for males dependences on attained age and age at exposure are the same as for all digestive cancers:

$$ERR(d,a,e) = 0.118d \exp\left[-0.0526 \min(\max(-15; e-30)) - 1.626 \max\left(0; \ln\frac{a}{50}\right)\right] \quad (6.8)$$

Models suggested by the BEIR VII Committee (BEIR, 2006) use common dependence on attained age and age at exposure for males and females:

$$ERR(d,a,e) = \beta_s d \exp\left[-0.03 \min(0; e-30) - 1.4 \max\left(0; \ln\frac{a}{60}\right)\right] \quad (6.9)$$

where β_s equals to 0.21 for males and 0.48 for females. The above models of BEIR (2006) are very similar to those suggested by Preston et al. (2007):

$$ERR(d,a,e) = \beta_s d \exp\left[-0.013 \min(0; e-30) - 1.5 \max\left(0; \ln\frac{a}{70}\right)\right] \quad (6.10)$$

where β_s is 0.21 for males and 0.47 for females.

All above shown models are compared with the model suggested for use in ProZES in the following Fig. 6.7–Fig. 6.8.

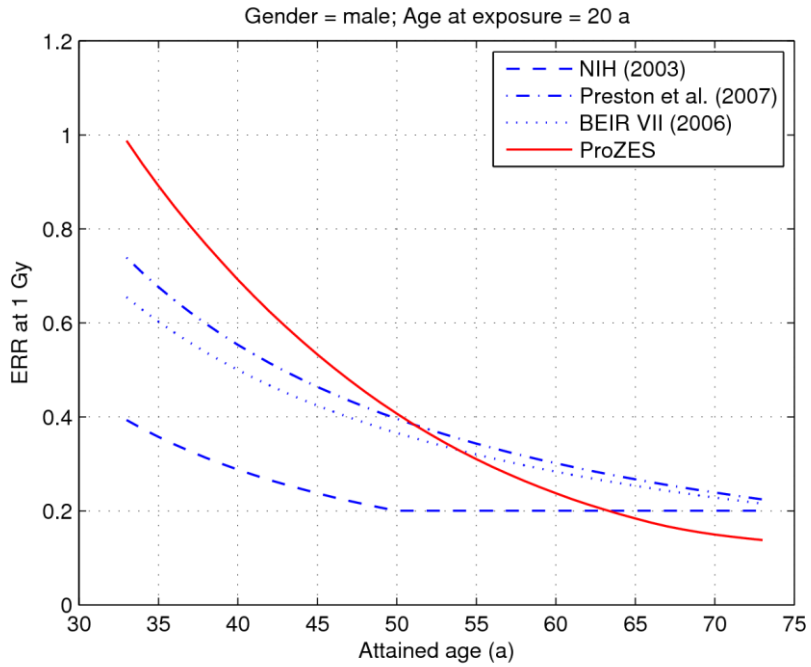

Fig. 6.7 Comparison of ERR models for male stomach cancer for age at exposure 20 years and for attained ages within 13 and 53 years after exposure.

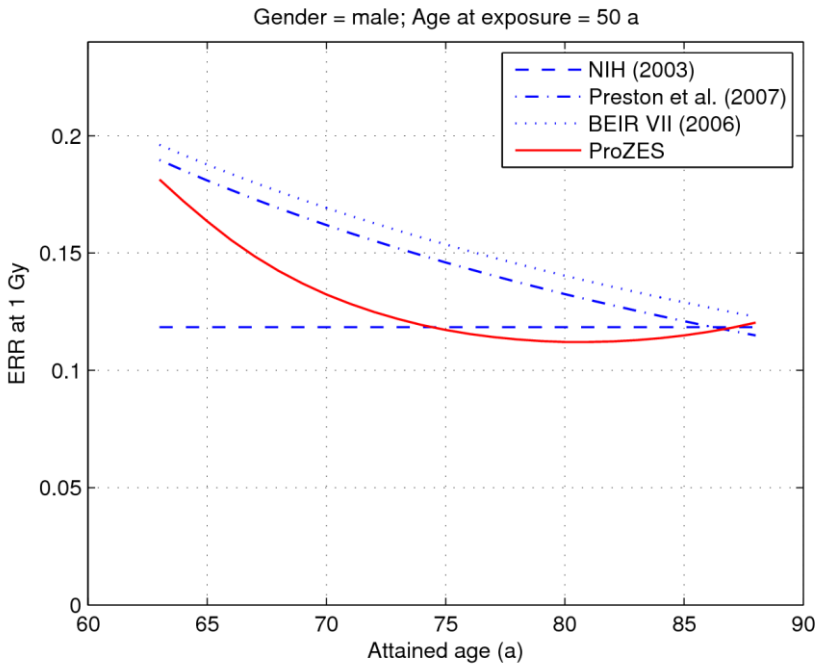

Fig. 6.8 Comparison of ERR models for male stomach cancer for age at exposure 50 years and for attained ages more than 13 years after exposure.

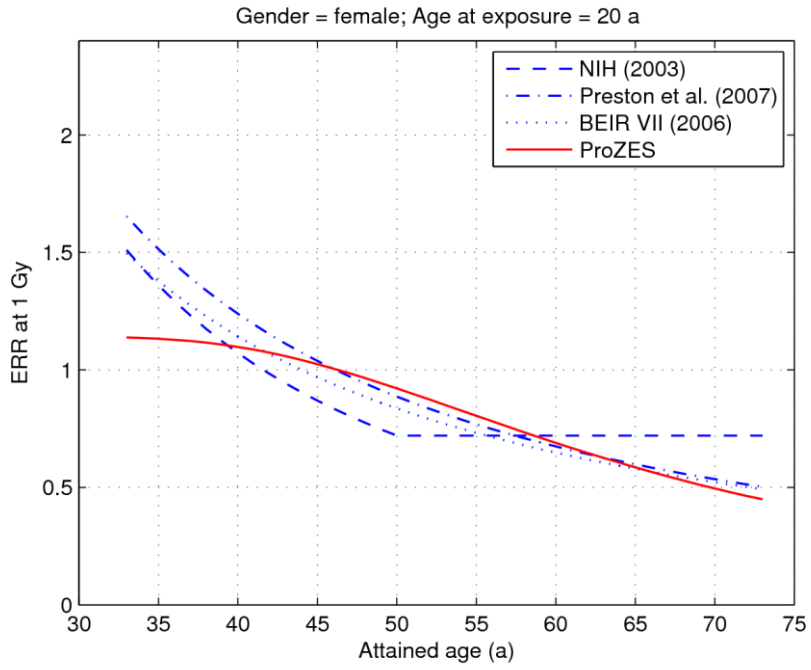

Fig. 6.9 Comparison of ERR models for female stomach cancer for age at exposure 20 years and for attained ages within 13 and 53 years after exposure.

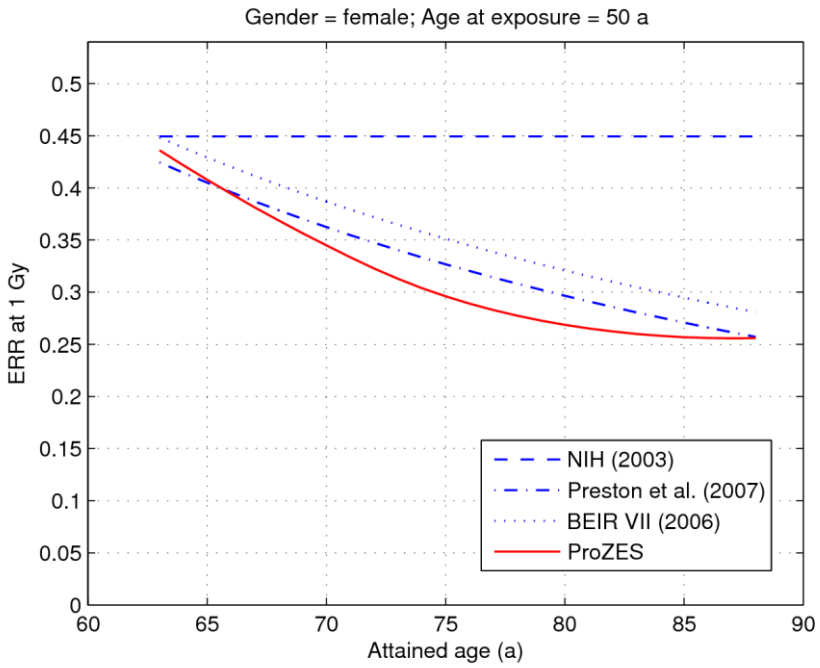

Fig. 6.10 Comparison of ERR models for female stomach cancer for age at exposure 50 years and for attained ages more than 13 years after exposure.

6.5. IREP/ProZES comparisons of assigned shares for stomach cancer

6.5.1. Single exposure

Calculations by ProZES have been done for low dose-rate 0.042 mGy h^{-1} (LDR) and high dose-rate ≥ 6 mGy h^{-1} (HDR). Alternative calculations made with on-line version of IREP-NCI are performed for both acute and chronic exposures. Total dose of single exposure equals to 1 Gy in all cases.

Calculated distributions for male are shown in Fig. 6.11 and their numerical values for selected percentiles are listed in Table 6.3. The similar comparisons for females are presented by Fig. 6.12 and Table 6.4.

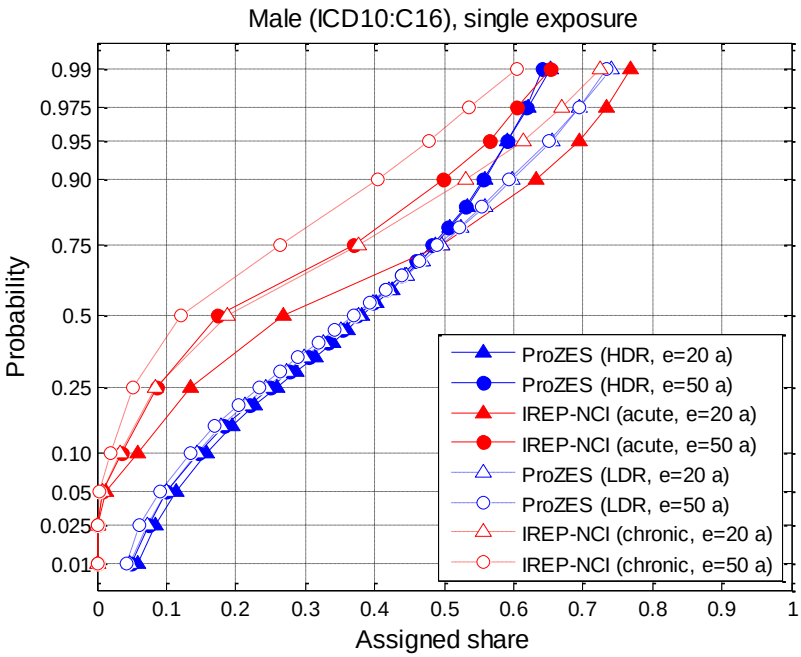

Fig. 6.11 Comparison of assigned share calculated using IREP-NCI (red symbols) and ProZES (blue symbols) for a male with stomach cancer diagnosed in 2006 at age 70 after single HDR-exposure (solid lines) or single LDR-exposure (dashed lines) with dose 1Gy at ages 20 (triangles, dashed lines) and 50 (circles, solid lines)

Table 6.3. Percentiles of distributions of Z for male stomach cancer at age 70 in 2006 after exposure at 1 Gy at ages 20 and 50.

Q	e=20 a				e=50 a			
	ProZES		IREP		ProZES		IREP	
	HDR	LDR	acute	chronic	HDR	LDR	acute	chronic
0.01	0.059	0.047	0.000	0.000	0.049	0.042	0.000	0.000
0.05	0.113	0.100	0.014	0.007	0.101	0.090	0.008	0.004
0.1	0.157	0.145	0.058	0.032	0.147	0.134	0.036	0.020
0.5	0.382	0.376	0.269	0.188	0.375	0.369	0.174	0.120
0.9	0.557	0.598	0.632	0.531	0.556	0.594	0.499	0.405
0.95	0.591	0.656	0.695	0.614	0.590	0.652	0.565	0.477
0.99	0.653	0.741	0.768	0.726	0.642	0.735	0.654	0.605

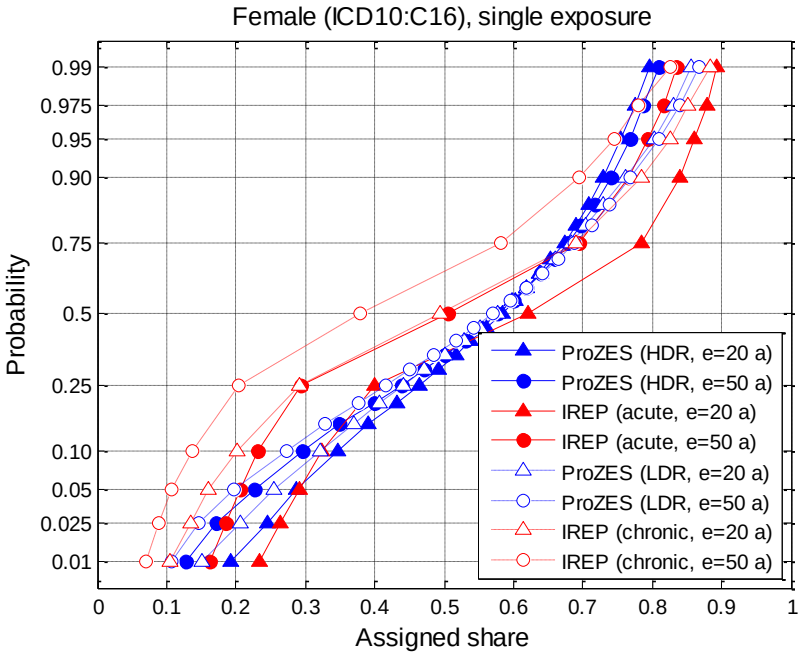

Fig. 6.12 Comparison of assigned share calculated using IREP-NCI (red symbols) and ProZES (blue symbols) for a female with stomach cancer diagnosed in 2006 at age 70 after single HDR-exposure(solid lines) or single LDR-exposure (dashed lines) with dose 1Gy at ages 20 (triangles, dashed lines) and 50 (circles, solid lines)

Table 6.4 Percentiles of distributions of Z for female stomach cancer at age 70 in 2006 after exposure at 1 Gy at ages 20 and 50

Q	e=20 a				e=50 a			
	ProZES		IREP		ProZES		IREP	
	HDR	LDR	acute	chronic	HDR	LDR	acute	chronic
0.01	0.193	0.150	0.233	0.106	0.128	0.107	0.162	0.069
0.05	0.286	0.254	0.292	0.160	0.226	0.197	0.206	0.107
0.1	0.346	0.322	0.324	0.203	0.295	0.273	0.231	0.137
0.5	0.584	0.577	0.620	0.494	0.578	0.570	0.506	0.379
0.9	0.729	0.762	0.841	0.786	0.740	0.768	0.766	0.695
0.95	0.754	0.804	0.861	0.826	0.768	0.811	0.794	0.746
0.99	0.795	0.857	0.892	0.885	0.809	0.868	0.836	0.825

6.5.2. Thirty years of protracted exposure

Comparisons of ProZES and IREP-NCI for multiple exposures are done for males and females after 30 annual exposures, starting age 20 years, with different dose rates. For ProZES – low dose rate 0.042 mGy h^{-1} and high dose-rate ≥ 6 mGy h^{-1}, and for IREP-NCI – acute and chronic exposures. In all comparisons it was assumed that the cancer was diagnosed in 2006 at age 70. Results of the comparisons are shown in Fig. 6.13 and Fig. 6.14, while numerical values are presented in Table 6.5.

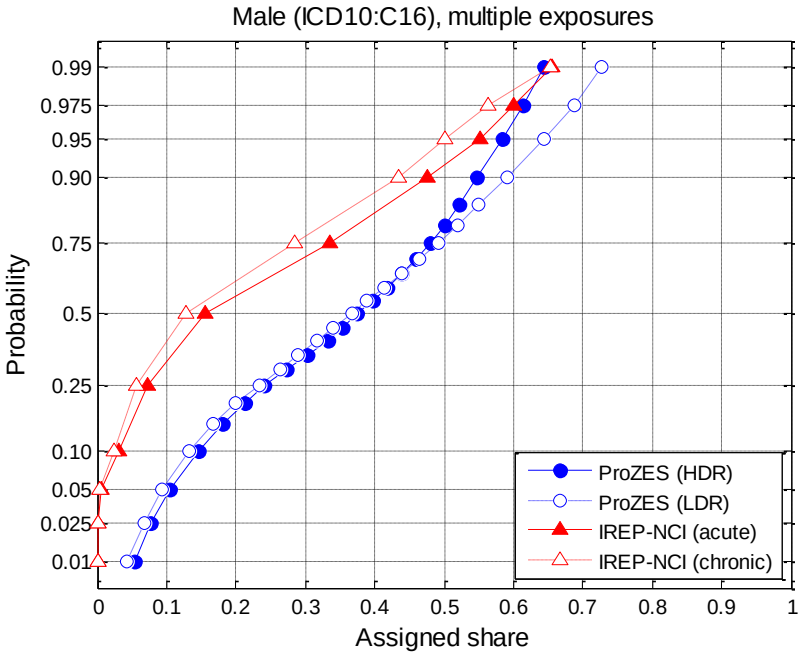

Fig. 6.13 Comparison of assigned share calculated using IREP-NCI (red symbols) and ProZES (blue symbols) for a male with stomach cancer diagnosed in 2006 at age 70 after 30 annual LDR- or HDR-exposures with total dose of 1 Gy starting at age 20 (for IREP: chronic and acute, respectively)

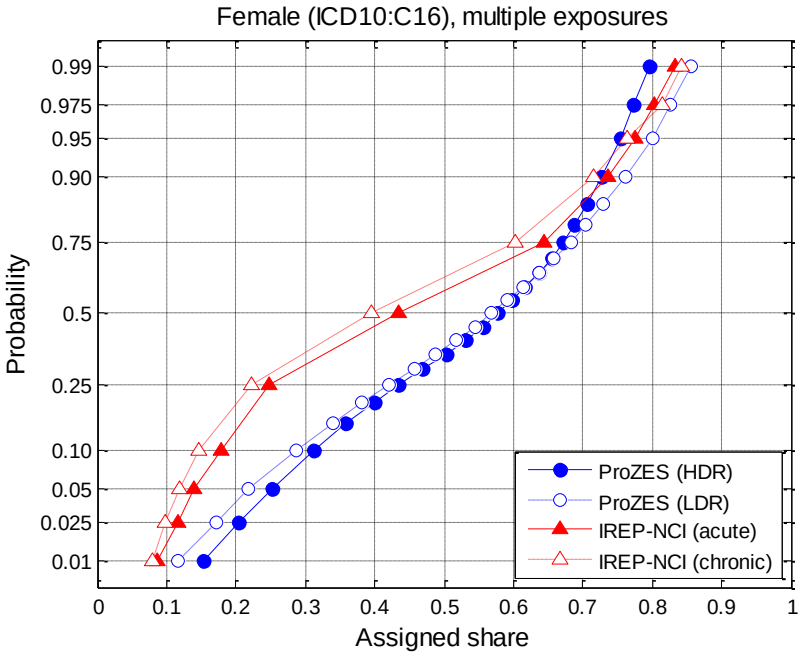

Fig. 6.14 Comparison of assigned share calculated using IREP-NCI (red symbols) and ProZES (blue symbols) for a female with stomach cancer diagnosed in 2006 at age 70 after 30 annual LDR- or HDR-exposures with total dose of 1 Gy starting at age 20 (for IREP: chronic and acute, respectively)

Table 6.5 Percentiles of distributions of Z for stomach cancer among males and females at age 70 in 2006 after 30 high and low dose-rate annual exposures with a total dose of 1 Gy starting at age 20.

Q	Male				Female			
	ProZES		IREP		ProZES		IREP	
	HDR	LDR	acute	chronic	HDR	LDR	acute	chronic
0.01	0.055	0.043	0.000	0.000	0.154	0.117	0.088	0.079
0.05	0.104	0.094	0.006	0.004	0.253	0.218	0.138	0.119
0.1	0.146	0.132	0.032	0.024	0.313	0.287	0.178	0.147
0.5	0.374	0.368	0.156	0.128	0.578	0.568	0.434	0.396
0.9	0.548	0.591	0.476	0.434	0.727	0.761	0.737	0.716
0.95	0.585	0.644	0.552	0.502	0.755	0.800	0.774	0.765
0.99	0.644	0.728	0.655	0.654	0.797	0.855	0.833	0.843

7. COLON CANCER (ICD10:C18)

7.1. Model description

For colon cancer, the age-attained dependence of the ERR in the LSS cohort differs significantly for males and for females. On the other hand, no biological mechanism is known that supports such a difference, no other study has demonstrated such a difference, and the baseline rates of males and females show a similar age dependence. In order to take both aspects into account it is proposed to apply a multi-model inference procedure: to select the best models from a set of gender-specific models and from those with common dependence on age at time of diagnosis and at time of exposure, and give them a subjectively chosen weight (in the following the same weight is given to both of the models, see Fig. 7.1).

Two approaches have been developed to select models that are taken into account in the multi-model inference (see Chapter 3), namely, selection criteria for nested models are based on minimum AIC value or on likelihood ratio test (LRT). Of a total of 46 models applied to the LSS data set for colon cancer, both selection criteria have led to a set of six models, of which five models being the same in both approaches (see Fig. 7.1). Then, both models different in both criteria were included in the final set of models, thus, multi-model inference was realized with a set of seven models.

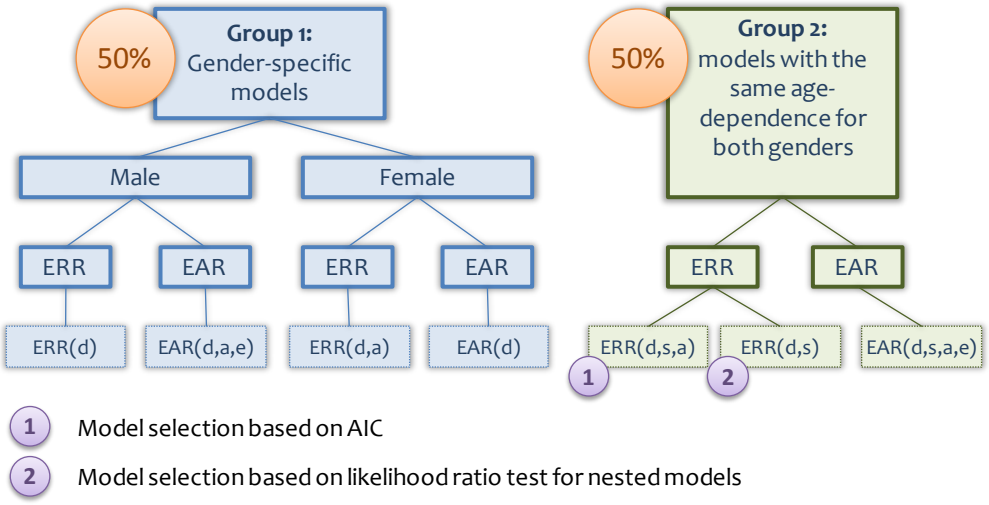

Fig. 7.1 Taxonomy of selection of colon cancer models for multi-model inference.

The multi-model inference was implemented in the following way. For the given gender, the final model is constructed from five models: two independent models from gender-specific models (Group 1) and three models from the group of models with common age dependence for both genders (Group 2). Weights of groups 1 and 2 are selected equal to 0.5 as there is no evidence to prefer either of the two groups.

The set of selected models along with their characteristics are summarized in Table 7.1 and described explicitly in the following sub-sections.

Table 7.1. Selected colon cancer risk models and their characteristics

Group	Model	Gender	No. of cases		K	AIC	Weight
			baseline	excess			
1	*ERR*(d)[a]	m	632.1	55.9	7	1223.3	0.5×0.9121=0.45605
1	*EAR*(d,a,e)[b]	m	634.4	53.5	9	1228.0	0.5×0.0879=0.04395
1	*ERR*(d,a)	f	800.3	19.7	9	1238.4	0.5×0.1096=0.0548
1	*EAR*(d)	f	805.9	14.1	8	1234.3	0.5×0.8904=0.4452
2	*ERR*(d,s)	m+f	1432.6	75.4	15	2464.6	0.5×0.4080=0.2040
2	*ERR*(d,s,a)[c]	m+f	1431.7	76.3	16	2464.0	0.5×0.5371=0.26855
2	*EAR*(d,s,a,e)	m+f	1434.5	73.5	17	2468.6	0.5×0.0549=0.02745

[a] 'constant' ERR model

[b] EAR model depends on attained age (a) and on age at exposure (e)

[c] ERR model with a scale factor depending on gender (s) and having common dependence on attained age (a) for both genders

7.2. Baseline

For all selected models (see Table 7.1) functional form of the fitted baseline is the same for the given gender. Baseline for males and females are slightly different and for males it is:

$$\lambda_{0,m} = \exp\left[\beta_0 + \beta_1 \ln\frac{a}{70} + \beta_2 \ln^2\frac{a}{70} + \beta_3 \max^2\left(0, \ln\frac{a}{\beta_4}\right) + \beta_7(e-30)\right], \qquad (7.1)$$

while for females there is an additional term with parameter β_8:

$$\lambda_{0,f} = \exp\left[\beta_0 + \beta_1 \ln\frac{a}{70} + \beta_2 \ln\frac{a}{70}^2 + \beta_3 \max^2\left(0, \ln\frac{a}{\beta_4}\right) + \beta_7(e-30) + \beta_8(e-30)^2\right] \qquad (7.2)$$

Parameters of the baseline functions are given in Table 7.2. Factor β_{city}, accounting for differences in baselines between the two cities, has been found insignificant and is set equal to zero.

Table 7.2. Parameters of baseline functions for the selected colon cancer models.

Model	Parameter						
	β_0	β_1	β_2	β_3	β_4	β_7	β_8
Group 1 – male							
ERR(d)	−5.5836	12.513	4.1526	−9.8817	53.60	−0.0713	–
EAR(d,a,e)	−5.5186	12.896	4.5514	−10.429	53.47	−0.0708	–
Group 1 – female							
EAR(d)	−6.6772	10.635	3.1439	−9.3033	59.69	−0.0608	4.34×10^{-4}
ERR(d,a)	−6.7953	9.6498	1.9637	−8.2620	62.08	−0.0590	3.69×10^{-4}
Group 2 – male							
EAR(d,s,a,e)	−5.5080	13.005	4.6323	−10.530	53.47	−0.0713	–
ERR(d,s)	−5.5836	12.513	4.1527	−9.8818	53.60	−0.0713	–
ERR(d,s,a)	−5.5782	12.575	3.9071	−9.7864	53.64	−0.0713	–
Group 2 – female							
EAR(d,s,a,e)	−6.7044	10.501	3.7446	−9.7891	60.30	−0.0589	3.82×10^{-4}
ERR(d,s)	−6.7332	10.256	3.6330	−9.6270	60.85	−0.0590	3.67×10^{-4}
ERR(d,s,a)	−6.7407	10.269	3.4968	−9.5641	60.93	−0.0590	3.69×10^{-4}

7.3. Excess risks

7.3.1. Group 1: gender-specific models

For males, the model with a constant ERR[3]

$$ERR(d) = \alpha_0 d = 1.0758\, d \tag{7.3}$$

and the model with an EAR depending on attained age and age at exposure

$$EAR(d,a,e) = \alpha_0\, d \exp\left(-\alpha_3(e-30) + \alpha_5 \ln\frac{a}{70}\right) = \\ = 1.579\times10^{-3}\, d \exp\left(-0.0818\,(e-30) + 7.805 \ln\frac{a}{70}\right) \tag{7.4}$$

are selected.

For females, the model with a constant EAR model

$$EAR(d) = \alpha_0 d = 1.0287\times10^{-4}\, d \tag{7.5}$$

and the model with ERR depending on attained age

$$ERR(d,a) = \alpha_0\, d \exp\left(\alpha_5 \ln\frac{a}{70}\right) = 0.2042\, d \exp\left(-4.914 \ln\frac{a}{70}\right) \tag{7.6}$$

are selected.

[3] Strictly speaking, "constant ERR model" is not constant as relative risk still depends on gender and dose. However, this name is used to stress the fact that in this model risk does not depend on age- and time-related factors and for given gender and dose value is represented by a constant

7.3.2. Group 2: models with age dependence common for both genders

This group consists from three models (see Fig. 7.1), namely, *ERR(d,s)*, *ERR(d,s,e)*, and *EAR(d,s,a,e)*, which parameters are listed below.

EAR model dependent on attained age and age at exposure appears as follows:

$$EAR(d,s,\mathrm{a},e) = \alpha_0\, d \exp\left(-\alpha_3(e-30) + \alpha_5 \ln\frac{a}{70} + \alpha_7 s\right) = \\ = 6.78\times 10^{-4}\, d \exp\left(-0.0718\,(e-30) + 6.706 \ln\frac{a}{70} - 0.784\, s\right) \tag{7.7}$$

ERR(d,s,a) is represented in the following way:

$$ERR(d,s,a) = \alpha_0\, d \exp\left(\alpha_5 \ln\frac{a}{70} + \alpha_7 s\right) = \\ = 0.555\, d \exp\left(-1.935 \ln\frac{a}{70} - 0.443\, s\right) \tag{7.8}$$

And constant ERR model is given by the following expression:

$$ERR(d,s) = \alpha_0 d \exp(\alpha_7 s) = 0.588\, d \exp(-0.6041\, s) = \begin{cases} 1.0758\, d, \text{ male} \\ 0.3214\, d, \text{ female} \end{cases} \tag{7.9}$$

All these partial models along with appropriately weighted composite model are shown in Fig. 7.2 and Fig. 7.3 for males and in Fig. 7.4 and Fig. 7.5 for females for ages at exposure 20 and 50 years. As seen from the figures, the combined model still shows significantly different age-dependence for different genders.

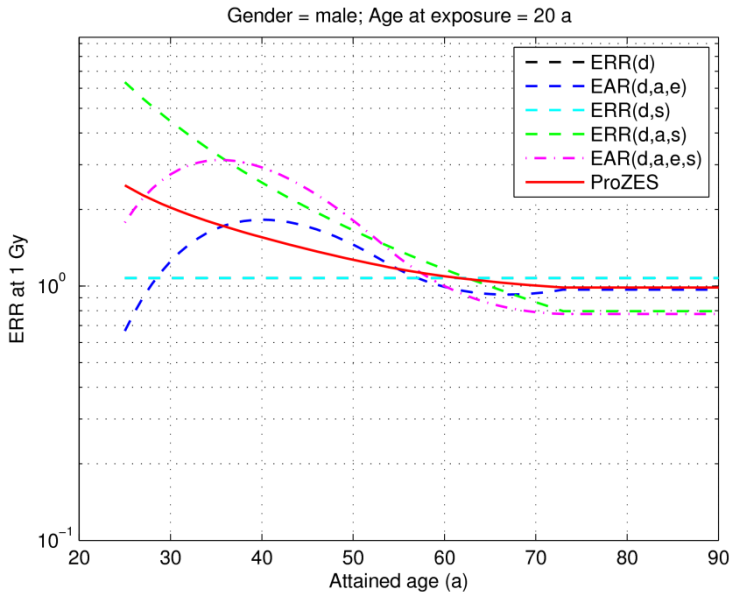

Fig. 7.2 Models for the excess relative colon cancer risk among males exposed at age 20. Dashed, dot-dashed, and dotted lines represent component models, red solid line shows a combined model built using multi-model inference.

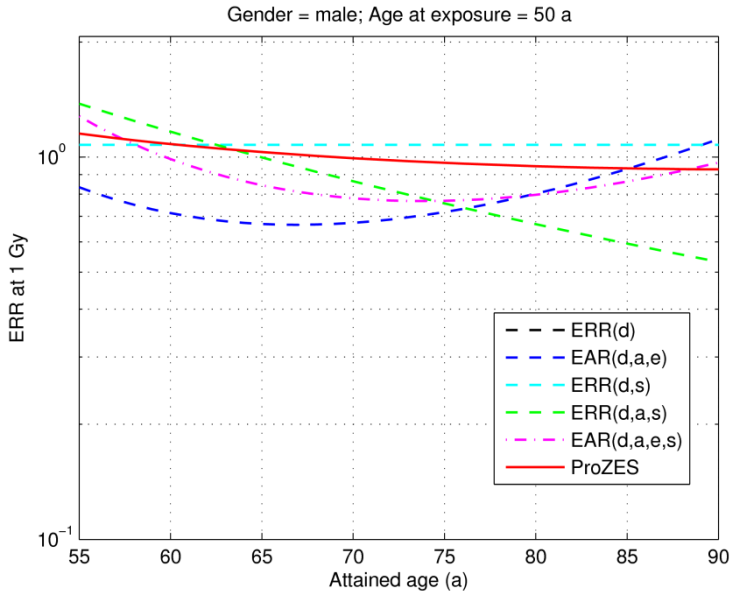

Fig. 7.3 Models for the excess relative colon cancer risk among males exposed at age 50. Dashed, dot-dashed, and dotted lines represent component models, red solid line shows a combined model built using multi-model inference.

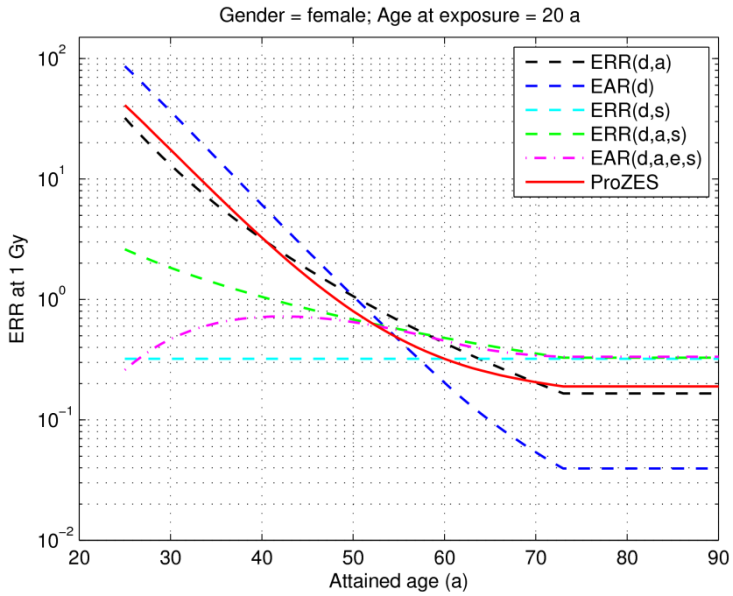

Fig. 7.4 Models for the excess relative colon cancer risk among females exposed at age 20. Dashed, dot-dashed, and dotted lines represent component models, red solid line shows a combined model built using multi-model inference.

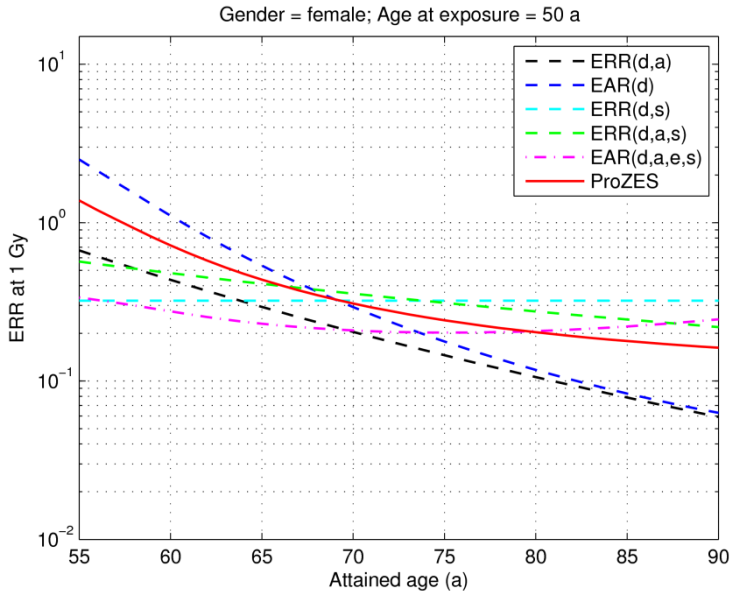

Fig. 7.5 Models for the excess relative colon cancer risk among females exposed at age 50. Dashed, dot-dashed, and dotted lines represent component models, red solid line shows a combined model built using multi-model inference.

7.4. Baseline colon cancer incidence in the LSS cohort and in Germany

Baseline for colon cancer in Germany is reported (RKI, 2010; GEKID, 2010) as a combined incidence for colorectal cancers (ICD10:C18-C21). For the LSS cohort, data for colon cancer (ICD10:C18) are reported, only. Thus, data from Bavarian cancer registry (Meyer et al., 2010) are used in this chapter to illustrate baseline incidence in Germany and to compare it to baselines in fitted models for the LSS cohort.

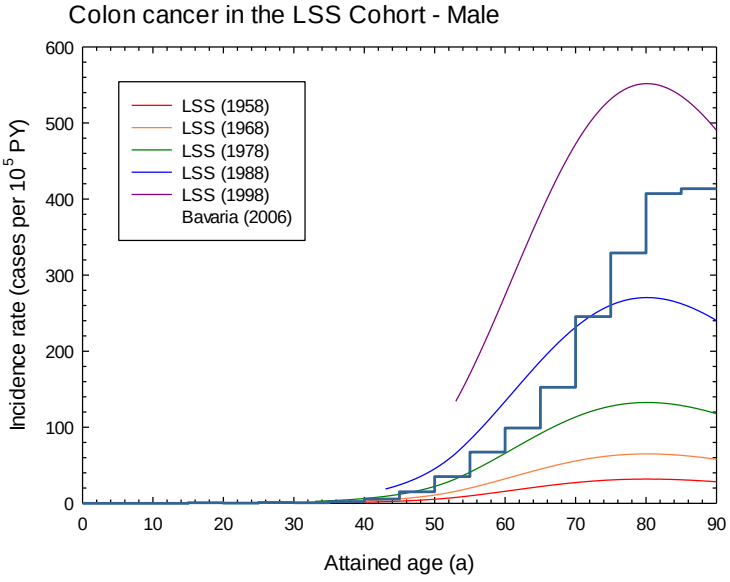

Fig. 7.6 Comparison of the fitted baseline of colon cancer among men in the LSS cohort in different years and that in Bavaria in 2006 (Meyer et al., 2010).

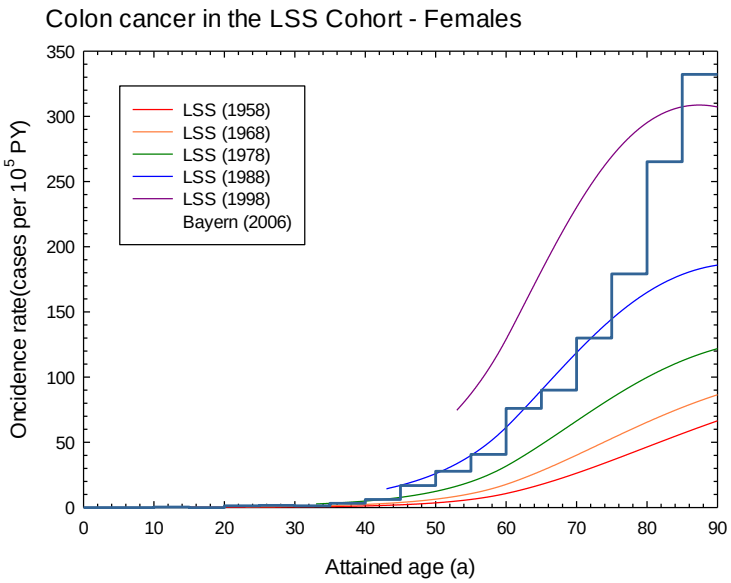

Fig. 7.7 Comparison of the fitted baseline of colon cancer among women in the LSS cohort in different years and that in Bavaria in 2006 (Meyer et al., 2010).

7.5. Comparison with other approaches

Best estimates of the ProZES ERR models for colon cancer are compared with models obtained by (Preston et al., 2007), adopted for IREP as described in (Land et al., 2003), and recommended by BEIR VII Report (BEIR, 2006). These models are described below and parameters' notations follow that from original publications.

The model recommended by BEIR Committee (BEIR, 2006) has the same attained age- and age at exposure dependences for both sexes:

$$ERR = \beta_s d \exp\left(\gamma \min(0, e-30) + \eta \ln\frac{a}{60}\right), \tag{7.10}$$

where $\beta_s = 0.63$ for males and $\beta_s = 0.43$ for females, $\gamma = -0.03$ and $\eta = -1.4$.

Model implemented in IREP (Land et al., 2003):

$$ERR = \alpha_s d \exp\left(\gamma \min(0, \max(-15, e-30)) + \delta \max\left(0, \ln\frac{a}{50}\right)\right), \tag{7.11}$$

where $\alpha_s = 0.5405$ for males and $\alpha_s = 0.6430$ for females, $\gamma = -0.05255$ and $\delta = -1.626$.

Model of Preston et al. (2007):

$$ERR = \alpha_s d \exp\left(-0.001(e-30) - 2.68 \ln\frac{a}{70}\right) \tag{7.12}$$

where $\alpha_s = 0.73$ for males and $\alpha_s = 0.34$ for females.

These models are compared with ProZES models based on multi-model inference as described above. Comparisons are shown on Fig. 7.8–Fig. 7.11 for male and females for ages at exposure 20 and 50 years.

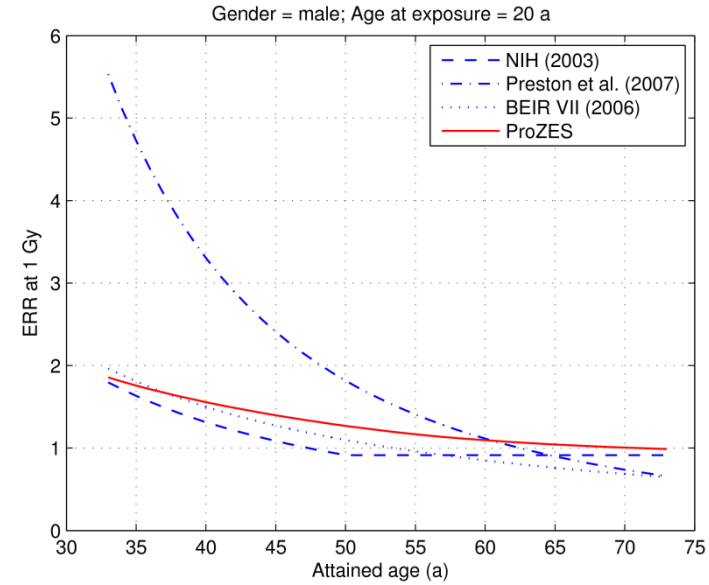

Fig. 7.8 Comparison of ERR models for male colon cancer for age at exposure 20 years and for attained ages within 13 and 53 years after exposure.

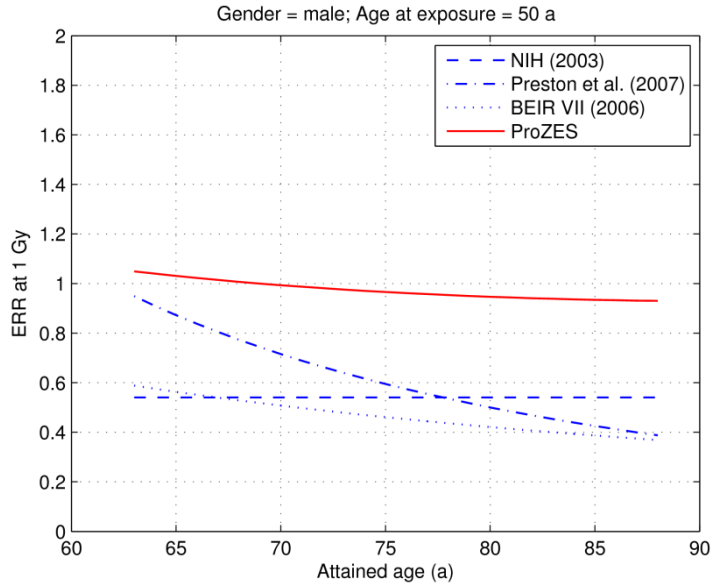

Fig. 7.9 Comparison of ERR models for male colon cancer for age at exposure 50 years and for attained ages more than 13 years after exposure.

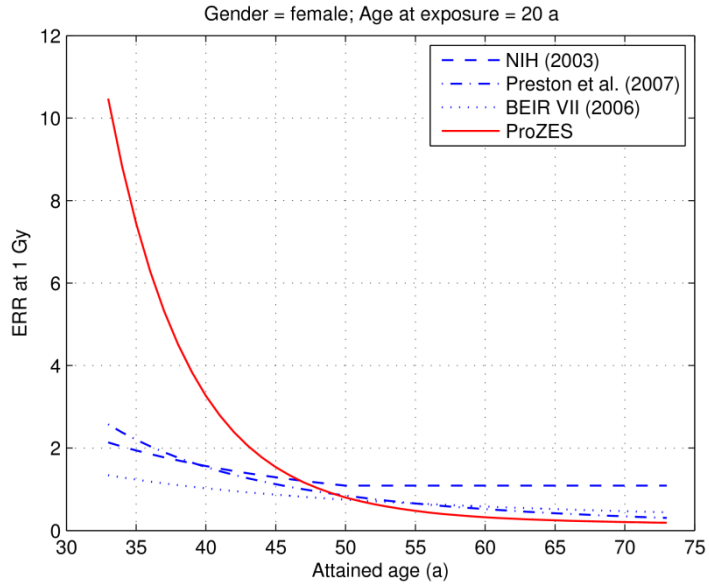

Fig. 7.10 Comparison of ERR models for female colon cancer for age at exposure 20 years and for attained ages within 13 and 53 years after exposure

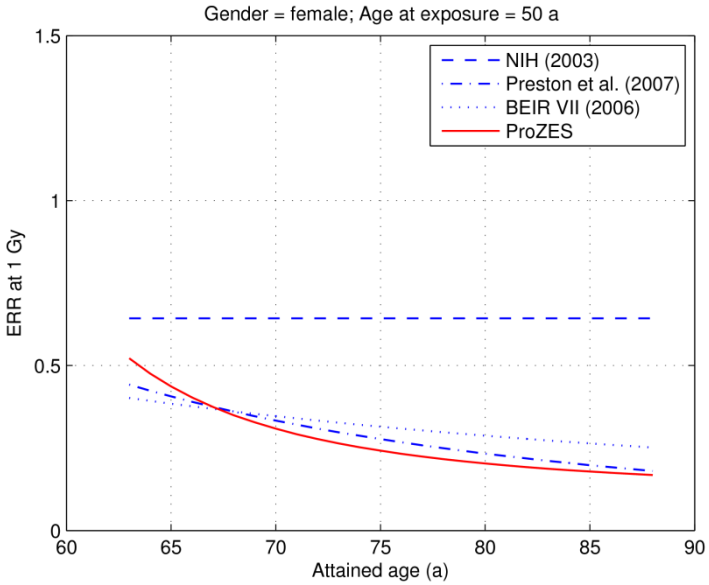

Fig. 7.11 Comparison of ERR models for female colon cancer for age at exposure 50 years and for attained ages more than 13 years after exposure

7.6. IREP/ProZES comparison for colon cancer

7.6.1. Single acute exposure

Shown on Fig. 7.12 and Fig. 7.13 are distributions of assigned share for colon cancer among male and female after single 1-Gy-exposure at ages 20 or 50 years, computed according to the ProZES approach and using on-line version of IREP-NCI. High dose-rate ≥ 6 mGy h^{-1} is assumed for ProZES estimates, and acute exposure for the estimate done with IREP-NCI.

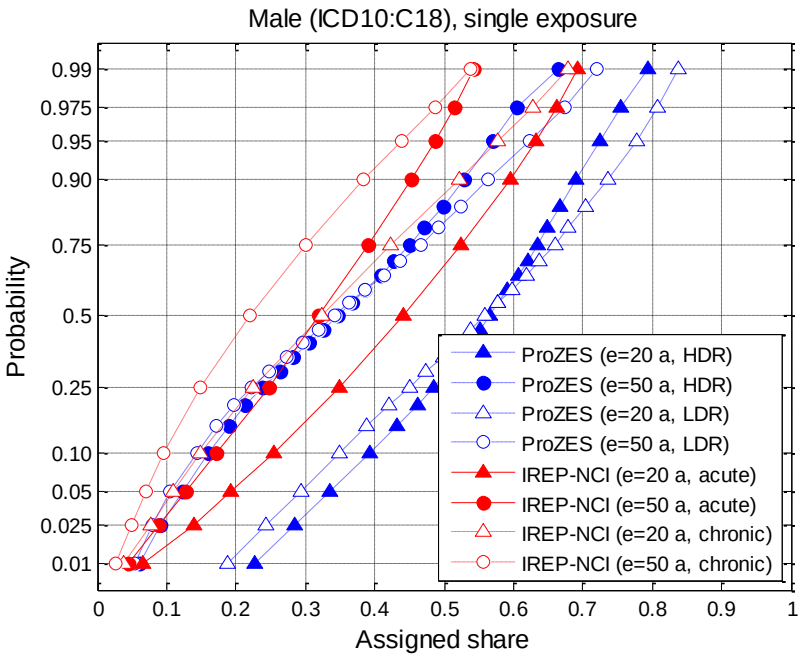

Fig. 7.12 Distributions of assigned share, Z, for a male, born in 1936, with colon cancer diagnosed in 2006, who was exposed to dose of 1 Gy with high dose-rate (solid lines) or low-dose-rate (dashed lines) at age 20 (triangles) and 50 (circles). Computations are done with IREP (red lines and symbols) and ProZES (blue lines and symbols).

Values of assigned share for selected quantiles are shown in Table 7.3 and Table 7.4.

Table 7.3. Percentiles of distribution of Z for a male with colon cancer diagnosed at age 70 in 2006 after single exposure with a dose of 1 Gy at ages 20 or 50.

Q	e=20 a				e=50 a			
	ProZES (HDR)	ProZES (LDR)	IREP (acute)	IREP (chronic)	ProZES (HDR)	ProZES (LDR)	IREP (acute)	IREP (chronic)
0.01	0.236	0.187	0.066	0.039	0.061	0.054	0.045	0.026
0.05	0.335	0.294	0.193	0.109	0.123	0.105	0.128	0.07
0.1	0.394	0.35	0.254	0.149	0.16	0.144	0.172	0.095
0.5	0.565	0.558	0.441	0.323	0.347	0.343	0.320	0.22
0.9	0.689	0.736	0.595	0.523	0.529	0.564	0.452	0.383
0.95	0.725	0.778	0.632	0.577	0.571	0.624	0.487	0.438
0.99	0.794	0.838	0.693	0.678	0.665	0.72	0.543	0.538

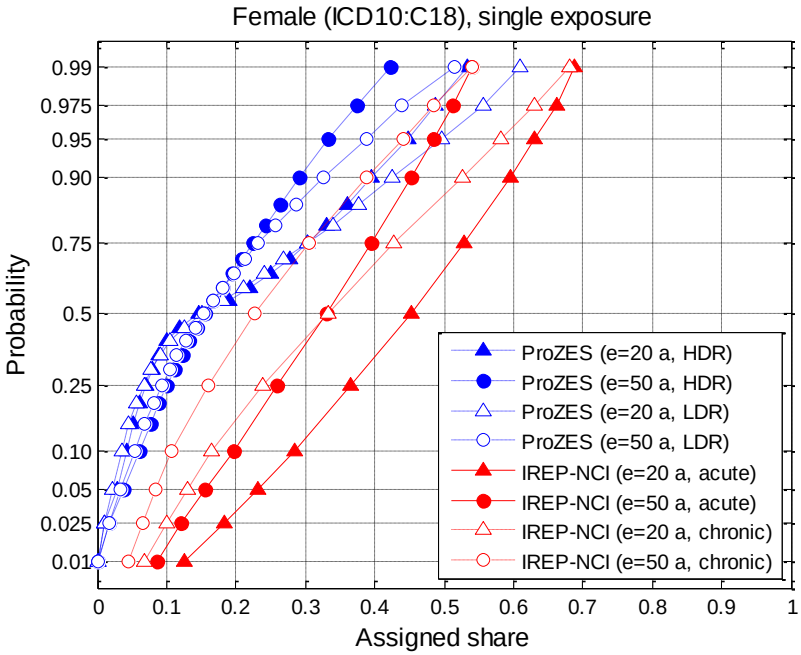

Fig. 7.13 Distributions of assigned share, Z, for a female, born in 1936, with colon cancer diagnosed in 2006, who was exposed to dose of 1 Gy with high dose-rate (solid lines) or low-dose-rate (dashed lines) at age 20 (triangles) and 50 (circles). Computations are done with IREP (red lines and symbols) and ProZES (blue lines and symbols).

Table 7.4. Percentiles of distribution of Z for a female with colon cancer diagnosed at age 70 in 2006 after single exposure with a dose of 1 Gy at ages 20 or 50.

Q	*e*=20 a				*e*=50 a			
	ProZES (HDR)	ProZES (LDR)	IREP (acute)	IREP (chronic)	ProZES (HDR)	ProZES (LDR)	IREP (acute)	IREP (chronic)
0.01	0	0	0.124	0.068	0	0	0.087	0.044
0.05	0.028	0.023	0.232	0.13	0.038	0.033	0.155	0.083
0.1	0.042	0.036	0.284	0.165	0.06	0.053	0.197	0.108
0.5	0.147	0.151	0.452	0.332	0.156	0.154	0.33	0.227
0.9	0.395	0.425	0.596	0.526	0.292	0.327	0.452	0.389
0.95	0.448	0.497	0.631	0.582	0.334	0.388	0.485	0.44
0.99	0.533	0.61	0.688	0.682	0.423	0.514	0.54	0.541

Impact of DREF correction on ERR estimates with colon cancer models selected for the ProZES is compared in the above figures with acute/chronic exposure treatment in IREP. Denoted in the figure as HDR is an exposure at high dose-rate (≥ 6 mGy h^{-1}), denoted as LDR is an exposure at low dose-rate of 0.042 mGy h^{-1}, typical to occupational exposures.

7.6.2. Thirty years of protracted exposure

Compared in Fig. 7.14 and Fig. 7.15 are assigned share distributions for multiple exposures. Namely, 30 exposures with total dose of 1 Gy, starting at age 20, have been evaluated by using the ProZES models and by IREP-NCI. ProZES estimates are shown for both LDR and HDR exposures.

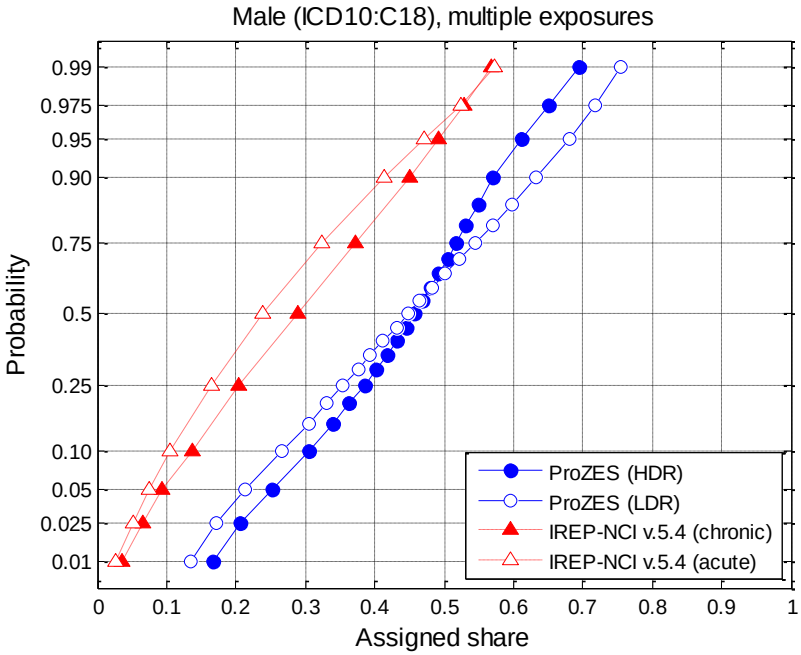

Fig. 7.14 Distributions of assigned share, Z, for a male, born in 1936, with colon cancer diagnosed in 2006 after 30 high-dose-rate (solid lines, filled symbols) or low dose-rate (dashed lines, empty symbols) annual exposures with a total dose of 1 Gy, starting at age 20.

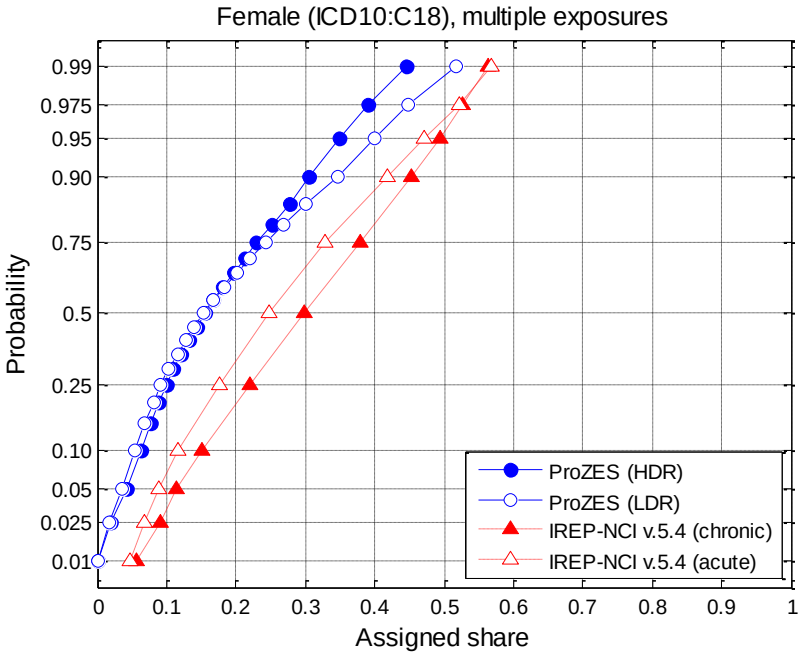

Fig. 7.15 Distributions of assigned share, Z, for a female, born in 1936, with colon cancer diagnosed in 2006 after 30 high-dose-rate (solid lines, filled symbols) or low dose-rate annual (dashed lines, empty symbols) exposures with a total dose of 1 Gy, starting at age 20.

Table 7.5. Percentiles of distributions of Z for colon cancer at age 70 in 2006 for males and females after 30 low dose-rate annual exposures with a total dose of 1 Gy starting at age 20.

Q	Male				Female			
	ProZES (HDR)	ProZES (LDR)	IREP (acute)	IREP (chronic)	ProZES (HDR)	ProZES (LDR)	IREP (acute)	IREP (chronic)
0.01	0.167	0.134	0.035	0.028	0	0	0.057	0.046
0.05	0.253	0.212	0.094	0.074	0.042	0.035	0.114	0.088
0.1	0.306	0.266	0.136	0.104	0.064	0.055	0.152	0.117
0.5	0.457	0.448	0.289	0.239	0.155	0.153	0.299	0.247
0.9	0.571	0.633	0.451	0.413	0.306	0.346	0.452	0.419
0.95	0.612	0.681	0.492	0.471	0.350	0.4	0.494	0.472
0.99	0.695	0.755	0.569	0.573	0.447	0.517	0.564	0.567

8. LUNG CANCER (ICD10:C34)

A decision was made to assess risk of radiation-induced lung cancer using the model of Furukawa et al. (2010) derived from an analysis of the LSS cohort.

Modelling the risk of lung cancer, diagnosed at age *a* in an individual of gender *s*, requires considering several carcinogenic factors, of which smoking and radiation exposure are the main ones. Correspondingly, the mathematical formulation of the risk model uses two sets of explanatory variables:

a) Radiation-related set, $D = \{d, e, t_d, \omega_R, ...\}$, where *d* is the radiation dose (Gy); *e* is the age at exposure; t_d is the duration of the exposure; ω_R is the radiation weighting factor (RBE or else); or other factors.
b) Smoking-related set, $S = \{\Pi, t_s, t_q, ...\}$, where Π is the smoking 'dose' (pack-year); t_s and t_q are years smoked and years since termination of smoking for ex-smokers, correspondingly. Alternative set of explanatory variables for smoking effect can use smoking intensity expressed via pack-years and smoking duration, $cpd = \frac{\Pi}{t_s} \times 20$ (cigarettes per day or cpd). Correspondingly, the set of explanatory variables is $S = \{cpd, t_s, t_q, ...\}$.

8.1. Model description

Following Furukawa et al. (2010), total relative risk of lung cancer is assumed to depend on various factors, of which radiation exposure and smoking are accounted for and modelled. Denoting effect of radiation exposure as $\rho(D)$, effect of smoking as $\phi(S)$, and total and baseline lung cancer incidence as λ and λ_0, correspondingly, then combined effect of both factors on baseline incidence can be described via either additive model (AM):

$$\lambda = \lambda_0(1 + \phi(S) + \rho(D)) \tag{8.1}$$

or multiplicative model (MM):

$$\lambda = \lambda_0(1 + \phi(S))(1 + \rho(D)) \tag{8.2}$$

If both factors are not independent and there is interaction between radiation exposure and smoking, then generalized additive model (GAM):

$$\lambda = \lambda_0\big(1 + \phi(S) + \rho(D)\omega(S)\big) = \lambda_0(1 + \phi(S) + \rho'(D,S)) \tag{8.3}$$

and generalized multiplicative model (GMM):

$$\lambda = \lambda_0\big(1 + \phi(S))(1 + \rho(D)\omega(S)\big) = \lambda_0(1 + \phi(S))(1 + \rho'(D,S)) \tag{8.4}$$

can be applied.

It follows from eqs. (8.1)–(8.4) that $\lambda_0$is the baseline incidence rate of lung cancer among never-smokers.

Table 8.1. Selection of models for risk of lung cancer using two groups of additive and multiplicative models from Furukawa et al. (2010)

Model	K	dev	AIC	Weight (%)
Simple models				
Additive (AM)	25	9428.75	9478.75	13.73
Multiplicative (MM)	25	9425.07	9475.07	86.27
Generalized models				
Additive (GAM)	27	9415.70	9469.70	6.21
Multiplicative (GMM)	27	9410.27	9464.27	93.79

Furukawa et al. (2010) have built their models using an extended LSS cohort, which included lung cancer cases being absent in the city at the time of bombing. Correspondingly, baseline was modelled by accounting for place of residence (Hiroshima or Nagasaki) and presence in either city at the time of detonation:

$$\lambda_0 = \exp\left[\beta_{0,s} + \beta_{city}(c-1) + \beta_1 \ln\frac{a}{70} + \beta_2 \ln^2\frac{a}{70} + \beta_7\frac{e-30}{10} + \beta_9(c)NIC\right] \quad (8.5)$$

where *c* is the city index

$$c = \begin{cases} 1, & \text{for Hiroshima} \\ 2, & \text{for Nagasaki} \end{cases} \quad (8.6)$$

and the index *NIC* ('not-in-the-city' status, see Chapter 2) equals to zero for 23.46% of the cohort members and equals to one, otherwise. In the total cohort, 28.8% of members were residents of Nagasaki, others resided in Hiroshima.

Modified radiation effect is modelled as follows:

$$\rho'(D,S) = \alpha_0 D \exp\left[\alpha_3\frac{e-30}{10} + \alpha_5 \ln\frac{a}{70} + \alpha_8 \ln\left(\frac{cpd}{20}+1\right) + \alpha_9 \ln^2\left(\frac{cpd}{20}+1\right) + \alpha_{10}s\right] \quad (8.7)$$

where *cpd* is the smoking intensity, i.e. the number of cigarettes smoked per day. Correspondingly, simple radiation-only effect is represented as $\rho(D) = \rho'(D,0)$.

Modelling function for the smoking effect, (S), depends on individual smoking habits. For never-smokers, the smoking effect is apparently zero:

$$\phi(S) = 0 \text{ and } \rho'(D,S) = \rho(D) \quad (8.8)$$

For current and past smokers (also called ever-smokers), modelling of smoking effect depends on availability of information on smoking habits. That is, when information on smoking habits is available, then the function for the smoking effect appears as follows:

$$\phi(S) = \frac{\Pi}{50}\exp\left[\delta_{1,s} + \delta_2\frac{e-30}{10} + \delta_3 \ln\frac{t_s}{50} + \delta_4 \ln^2\frac{t_s}{50} + \delta_5 \ln(t_q+1)\right] \quad (8.9)$$

where Π is the smoking 'dose' (pack-year), t_s is the smoking duration (year), t_q is the number of years since quit smoking for ex-smokers. For persons with unknown smoking status, the average smoking effect is modelled as a constant factor:

$$\phi(S) = \exp(\delta_0) \tag{8.10}$$

where δ_0 is a constant dependent on gender and birth cohort (expressed in case of the LSS cohort via age-at-exposure *e*).

8.2. Radiation-related risk of lung cancer

Based on Eqs. (8.1)-(8.4), relative risk of radiation-induced lung cancer can be expressed as follows:

$$RR(D,S) = \frac{\lambda}{\lambda_0\big(1+\phi(S)\big)} \tag{8.11}$$

i.e. for additive (Eq. (8.3)) and multiplicative (Eq. (8.4)) models equations for relative risk are different:

$$RR(D,S) = \frac{1+\phi(S)+\rho'(D,S)}{1+\phi(S)} \text{ (additive)}, \tag{8.12}$$

$$RR(D,S) = 1+\rho'(D,S) \text{(multiplicative)}. \tag{8.13}$$

Excess relative risk due to radiation is correspondingly:

$$ERR_{rad} = \frac{\rho'(D,S)}{1+\phi(S)} \text{ (additive)}, \tag{8.14}$$

$$ERR_{rad} = \rho'(D,S) \text{ (multiplicative)}. \tag{8.15}$$

Applying multi-model inference, one gets for generalized models with non-zero interaction between radiation and smoking:

$$ERR_{rad,G} = \rho'(D,S)\left(\frac{W_A}{1+\phi(S)} + W_M\right) \tag{8.16}$$

and for simple models with independently acting radiation and smoking factors

$$ERR_{rad,S} = \rho(D)\left(\frac{W_A}{1+\phi(S)} + W_M\right), \tag{8.17}$$

where w_A and w_M are AIC-weights of additive and multiplicative models, correspondingly.

Examples of simple (Eqs. (8.1) and (8.2)) and generalized (Eqs. (8.3) and (8.4)) functions are shown in Fig. 8.1 for both genders. Both simple and generalized models are built from two components – additive and multiplicative. These components and their respective AIC weights are shown for simple models in Fig. 8.2; for generalized models – in Fig. 8.3.Fig. 8.3 Additive and multiplicative components for generalized models for males (left) and females (right) and their corresponding AIC weights

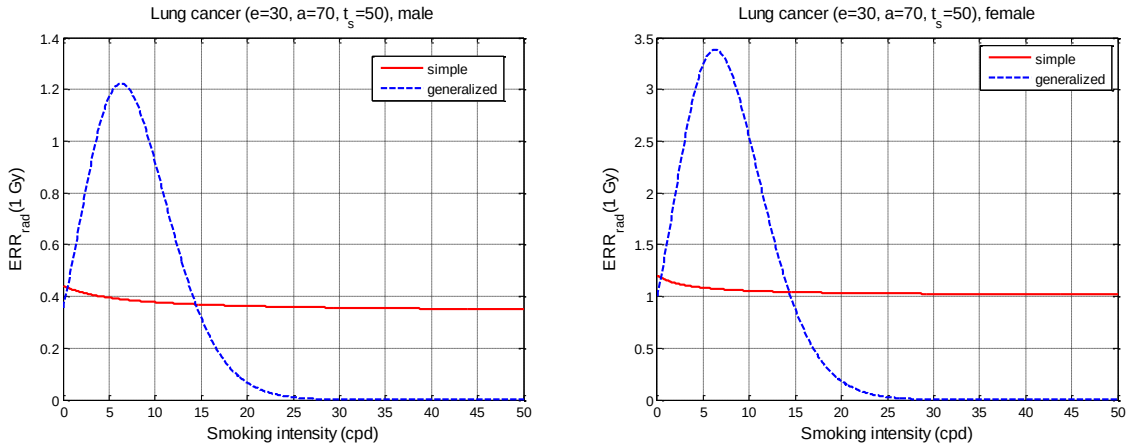

Fig. 8.1 Radiation-only excess relative risk of lung cancer for smoking males (left) and females (right) as function of smoking intensity (shown are AIC-weighted simple (8.1)-(8.2) and generalized (8.3)-(8.4) models)

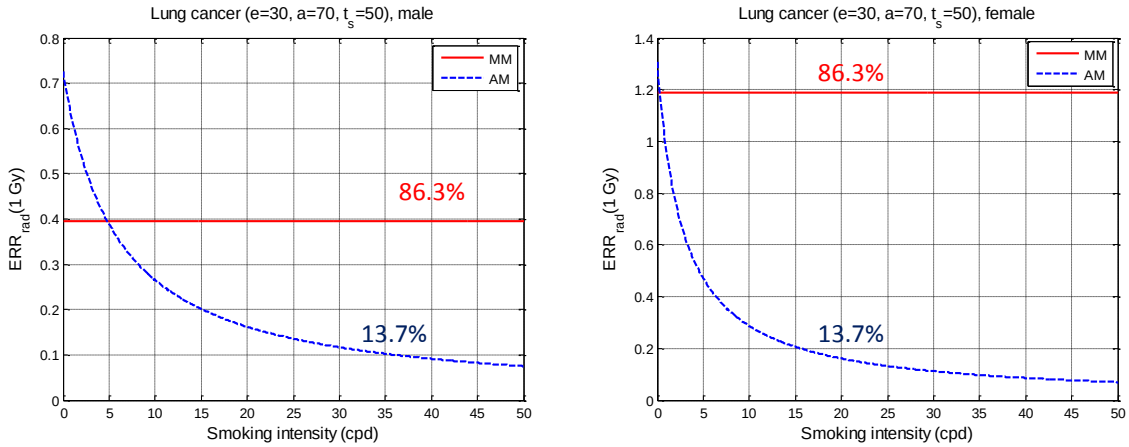

Fig. 8.2 Additive and multiplicative components for simple models for males (left) and females (right) and their corresponding AIC weights

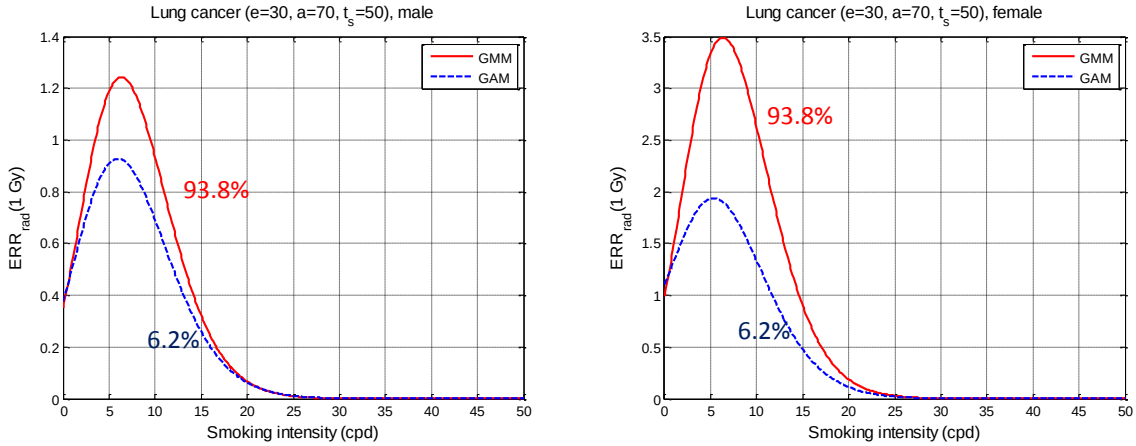

Fig. 8.3 Additive and multiplicative components for generalized models for males (left) and females (right) and their corresponding AIC weights

Depending on final form of the lung cancer risk model, additional epidemiological data might be required to characterize smoking habits of the German population.

8.3. Transfer of lung cancer risk from LSS-AHS cohort to German population

The model for ERR accepted for implementation in ProZES takes into account radiation and smoking effects, thus the baseline incidence rate is defined for non-exposed never-smokers. Unfortunately, these data are not readily available for the target group – the German population. That is why only uncertainty of transfer factor (see Eq.(5.8)) is modelled with an assumption that the ratio of baselines is log-uniformly distributed in range from 1/3 to 3.

8.4. Model of radiation-related ERR of lung cancer for ProZES

For use in ProZES, the following model is suggested (see also Fig. 8.4):

$$ERR_{rad} = \max\left(ERR_{rad,S}, ERR_{rad,G}\right) \tag{8.18}$$

which combines both simple and generalized models, thus providing a plausible trade-off (compromise) between very low *ERR* at high smoking intensities typical for generalized models and the fact that simple models are unable to express possible interaction between radiation and smoking (which was found to be significant in AIC sense).

The presently implemented model treats the whole radiation dose as created due to occupational exposure in the work place. Additional exposure to radon and daughters either common in houses or occupational for miners is not accounted for. Extension of the lung cancer model with radon-specific radiation exposure of lung tissue is anticipated during the second phase of the ProZES development.

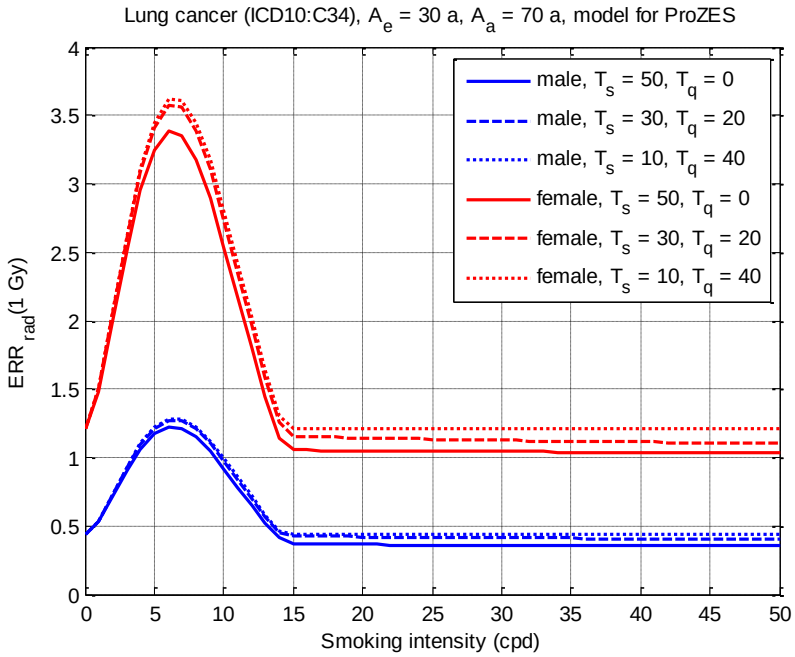

Fig. 8.4 Model for radiation ERR for lung cancer selected for ProZES for males (blue lines) and females (red lines) and various smoking habits as a function of smoking intensity

Implementation of the model of lung cancer ERR depends on availability of information on personal smoking habits. If such information is absent, then ProZES accounts for German-specific behavioral patterns regarding smoking based on reports of RKI (Schultz and Lampert, 2006; Lampert, 2011). If personal smoking status is unknown, then random sampling is applied to decide whether the person

should be regarded as never-smoker (35% of males and 53% of females) or ever-smoker (65% of males and 47% of females), for which average smoking habits are assumed based on personal age and birth cohort (see Table 8.2 and Table 8.3 below).

Table 8.2 Adopted average smoking intensity for smokers in Germany based on data from (Schultz and Lampert, 2006)

Age	Gender-averaged smoking intensity (cpd)	
	Males	Females
18–19	13.3	10.3
20–29	15.6	12.0
30–39	18.5	14.3
40–49	20.2	15.6
50–59	18.6	14.4
60–69	16.3	12.5
70–79	11.0	8.4

Table 8.3 Gender-specific median ages of start and quit smoking in Germany for various birth cohorts based on data from (Schultz and Lampert, 2006)

Birthyear	Start smoking		Quit smoking	
	male	female	male	female
1921-25	20	22	≈55	≈63
1941-45	19	20–21	≈55	≈63
1961-65	17	16.5	≈55	≈50–55
1976-80	16	16	n.d.	n.d.

For never-smokers only generalized models (8.3)-(8.4) are used because generalized models are preferable in AIC sense and without smoking term they are indistinguishable from simple ones.

8.5. IREP/ProZES comparisons

Two versions of the IREP program, NCI-IREP (Kocher et al. 2008) and NIOSH-IREP (NIOSH, 2009), use different approaches to calculate risk of lung cancer after radiation exposure. Lung cancer model implemented in NCI-IREP is based on analysis of the LSS cohort in 1950–1994 done by Pierce et al. (2003). At the same time, the lung cancer model described by Land et al. (2003) was the first adopted for the IREP program and it is still a default NIOSH model for lung cancer. This model had been developed using the LSS cohort data for shorter follow-up period: 1950–1990. The NIOSH version of IREP calculates lung cancer risk using both models: the models of NCI-IREP and of NIOSH-IREP; however, the maximum value of 99%-ile of assigned share is taken as the final estimate.

The model of Furukawa et al. (2010) implemented in ProZES and described above is also based on the LSS data; however, it is based on more recent incidence data for the follow-up period from 1958 to 1999. Because of apparent differences in implementation of the models, it is complicated to perform

reasonable comparison of the results obtained with different programs and models. For example, different parameterization of smoking habits makes comparisons of results from different programs less comparable.

Results for only a few situations are shown in Fig. 8.5–Fig. 8.8. As seen from the figures, the most significant difference between ProZES and IREP-NCI program is opposite dependence on 'age-at-exposure' effect. The lung cancer model of NIOSH does not include age effects at all (NIOSH, 2002), which is seen from Fig. 8.5 and Fig. 8.6 for never-smoking males and females. On the other hand, because the final approach adopted by the IREP-NIOSH assumes use of a model which predict higher assigned share, on Fig. 8.7 and Fig. 8.8 for current smokers IREP-NIOSH ends up with NIOSH model for age at exposure 50, while for age at exposure 20 it reproduces percentiles of the IREP-NCI program.

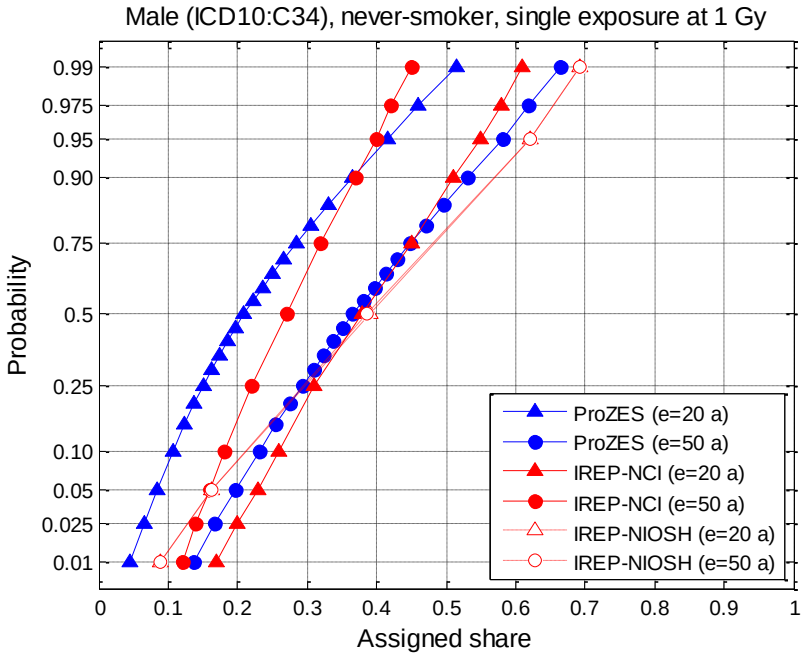

Fig. 8.5 Assigned share of radiation in lung cancer at age 70 for male never-smoker after single acute (HDR) exposure at age 20 (triangles) and 50 (circles) as computed by ProZES (blue lines and symbols), IREP-NCI (red closed symbols and lines), and IREP-NIOSH (red open symbols and lines)

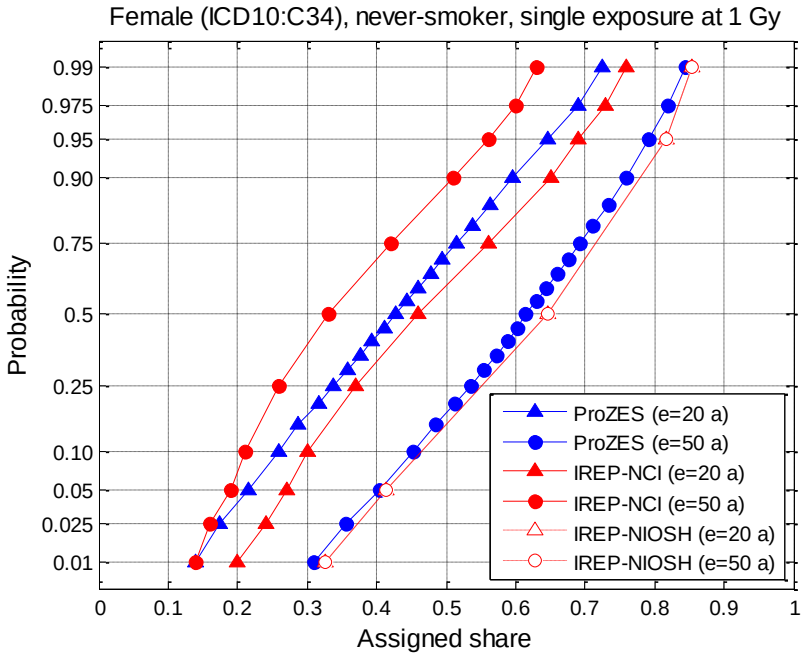

Fig. 8.6 Assigned share of radiation in lung cancer at age 70 for female never-smoker after single acute (HDR) exposure at age 20 (triangles) and 50 (circles) as computed by ProZES (blue lines and symbols), IREP-NCI (red closed symbols and lines), and IREP-NIOSH (red open symbols and lines)

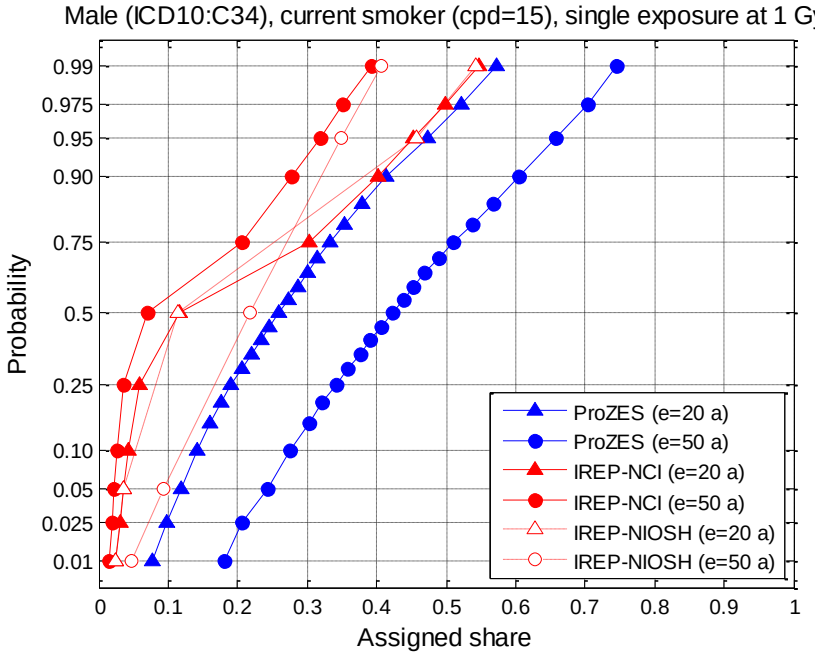

Fig. 8.7 Assigned share of radiation in lung cancer at age 70 for male current smoker (cpd=15 since age 18) after single acute (HDR) exposure at age 20 (triangles) and 50 (circles) as computed by ProZES (blue lines and symbols), IREP-NCI (red closed symbols and lines), and IREP-NIOSH (red open symbols and lines)

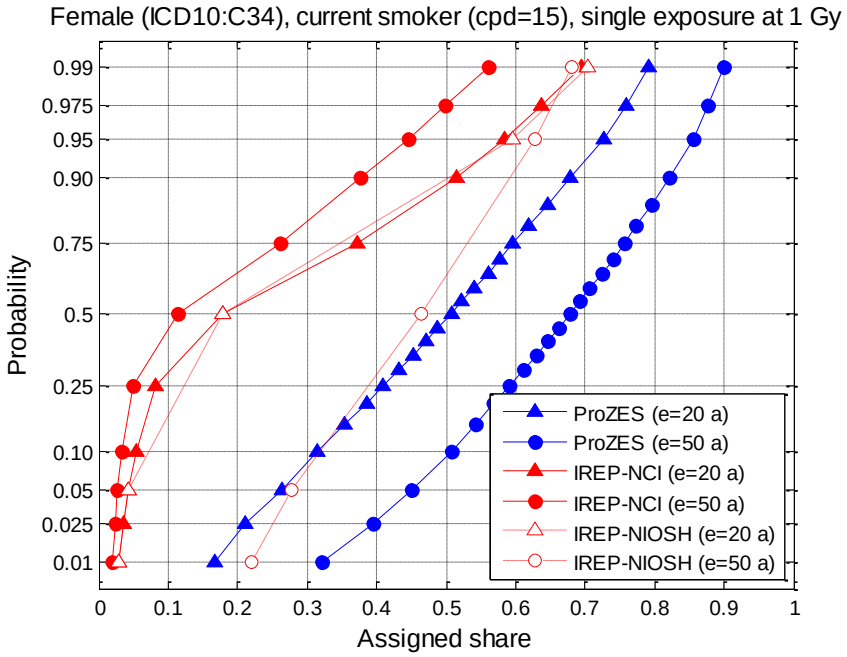

Fig. 8.8 Assigned share of radiation in lung cancer at age 70 for female current smoker (cpd=15 since age 18) after single acute (HDR) exposure at age 20 (triangles) and 50 (circles) as computed by ProZES (blue lines and symbols), IREP-NCI (red closed symbols and lines), and IREP-NIOSH (red open symbols and lines)

In general, excluding different dependence on age at exposure, the results obtained with ProZES come close to the results of IREP variants for never-smokers. At the same time, ProZES produces higher values of assigned share for current smokers as seen in Fig. 8.7 and Fig. 8.8. This can be explained by effects of generalized risk models (8.12) and (8.13), which introduce an interaction term between radiation and smoking, thus increasing the risk of radiation-induced cancer for smokers as a non-linear function of smoking intensity (see Fig. 8.4). Indeed, as seen from Fig. 8.4, radiation-related ERR is maximal for smoking intensity approx. 7 cigarettes per day. For such smoking intensity, median values of assigned share for the model adopted in ProZES become maximal as well: for males and age at exposure 20 median of assigned share increases from 0.25 (*cpd*=15) to 0.46 (*cpd*=7), for males and age at exposure 50 median of assigned share changes from 0.41 (*cpd*=15) to 0.66 (*cpd*=7), for females corresponding values are 0.50 (*cpd*=15, *e*=20), 0.70 (*cpd*=7, *e*=20), 0.67 (*cpd*=15, *e*=50), and 0.84 (*cpd*=7, *e*=50).

Table 8.4 Comparison of assigned share of radiation in lung cancer for never-smoker as computed by ProZES and IREP in implementations of NIH-NCI and NIOSH

Q	*e*=20			*e*=50		
	ProZES	IREP-NCI	IREP-NIOSH	ProZES	IREP-NCI	IREP-NIOSH
Male						
0.01	0.046	0.175	0.088	0.137	0.120	0.088
0.05	0.084	0.229	0.162	0.197	0.158	0.162
0.1	0.106	0.258	–	0.232	0.180	–
0.5	0.209	0.381	0.386	0.366	0.268	0.386
0.9	0.365	0.508	–	0.532	0.367	–
0.95	0.417	0.546	0.621	0.582	0.396	0.621
0.99	0.514	0.611	0.692	0.665	0.448	0.692
Female						
0.01	0.139	0.205	0.326	0.310	0.141	0.326
0.05	0.215	0.265	0.413	0.404	0.185	0.413
0.1	0.259	0.300	–	0.453	0.211	–
0.5	0.427	0.455	0.646	0.615	0.329	0.646
0.9	0.596	0.646	–	0.759	0.511	–
0.95	0.647	0.693	0.817	0.792	0.561	0.817
0.99	0.725	0.759	0.854	0.854	0.629	0.854

Table 8.5 Comparison of assigned share of radiation in lung cancer for current smoker (smoking intensity 15 cpd) as computed by ProZES and IREP in implementations of NIH-NCI and NIOSH

Q	*e*=20			*e*=50		
	ProZES	IREP-NCI	IREP-NIOSH	ProZES	IREP-NCI	IREP-NIOSH
Male						
0.01	0.078	0.025	0.024	0.181	0.016	0.047
0.05	0.118	0.035	0.035	0.243	0.022	0.094
0.1	0.141	0.042	–	0.276	0.027	–
0.5	0.259	0.117	0.115	0.423	0.070	0.218
0.9	0.413	0.4020	–	0.605	0.278	–
0.95	0.473	0.453	0.458	0.658	0.318	0.349
0.99	0.572	0.547	0.542	0.745	0.394	0.406
Female						
0.01	0.167	0.030	0.028	0.322	0.019	0.220
0.05	0.263	0.043	0.043	0.451	0.027	0.279
0.1	0.315	0.053	–	0.508	0.033	–
0.5	0.507	0.179	0.178	0.678	0.113	0.464
0.9	0.679	0.515	–	0.822	0.377	–
0.95	0.726	0.584	0.595	0.855	0.445	0.628
0.99	0.791	0.696	0.704	0.900	0.560	0.680

9. BREAST CANCER (ICD10:C50)

9.1. LSS, incidence 1958–1998, DS02

An empirical model developed by Kaiser et al. (2011) has been fit using data for LSS cohort members with doses less than 4 Gy. The model uses the following representation for the baseline:

$$\lambda_0 = \exp\left(\beta_0 + \beta_1 \ln\frac{a}{70} + \beta_2 \ln^2\frac{a}{70} + \beta_k \max^2\left(0, \ln\frac{a}{a_k}\right) + \beta_e(e-30)\right) \tag{9.1}$$

and for the excess relative risk:

$$ERR(a,e,d) = k_1 d \exp\left(\omega_a \ln\frac{a}{70} - \omega_e(e-30)\right). \tag{9.2}$$

For members of the LSS cohort with doses less than 4 Gy the fits of Kaiser et al. (2011) resulted in negligible/no dependence of the excess relative risk on age at exposure, thus the final model looks as follows:

$$ERR(a,d) = 0.93d \exp\left(-2.1 \ln\frac{a}{70}\right). \tag{9.3}$$

The resulting model (9.3) is similar to the model derived by Preston et al. (2007) for the LSS cohort:

$$ERR(a,d) = 0.87d \exp\left(-2.3 \ln\frac{a}{70}\right). \tag{9.4}$$

9.2. IREP model

The model adopted in IREP for female breast cancer risk (Land et al., 2003) is:

$$ERR = \alpha \exp\left(\gamma \min(0, \max(-15, e-30)) + \delta \min\left(0, \ln\frac{a}{50}\right)\right) \tag{9.5}$$

where $\alpha = 1.0213$, $\gamma = -0.03722$, and $\delta = -2.006$.

9.3. Pooled study

The pooled study (Preston et al., 2002) suggested the following EAR-model (EAR per 10^4 PY):

$$EAR(a,e,d) = \beta d \exp\left(\frac{\theta}{10}(e-25) + \gamma_1 \ln\frac{a}{50} + \gamma_2 \max\left(0, \ln\frac{a}{50}\right)\right) \tag{9.6}$$

where parameters of Eq. (9.6) and their covariances are given in Table 9.1 (Preston, 2010). Diagonal elements of the covariance matrix represent variances of the parameters.

Table 9.1. Parameters of the EAR model (9.6) (Preston et al., 2002; Preston, 2010)

Parameter	Value	Covariance			
		β	θ	γ_1	γ_2
β	9.74	2.5811			
θ	−0.51	0.078078	0.00991		
γ_1	3.5	0.33353	−0.018353	0.38194	
γ_2	−2.47	−1.0913	−0.011519	−0.46549	1.0273

The model suggested in the BEIR VII Report (BEIR, 2006) is:

$$ERR(a,d) = 0.51d \exp\left(-2 \ln \frac{a}{60}\right), \tag{9.7}$$

which is reportedly based on the pooled study (Preston et al., 2002) of breast cancer risk.

9.4. Model suggested for ProZES

The risk model implemented in ProZES is based on the model of the pooled study (Preston et al., 2002) with later modifications (Preston, 2010). The model (9.6) describes excess absolute risk; correspondingly, excess relative risk in the target population is estimated by dividing EAR from Eq. (9.6) by the baseline incidence rate observed in Germany in the year the cancer was diagnosed. In the following Fig. 9.1 and Fig. 9.2 the accepted model (solid green line), estimated for conditions in Germany in 2006, is shown in comparison with other models shown in this section above for females exposed at age 20 and 50, correspondingly. Fluctuations of ERR observed in Fig. 9.1 and Fig. 9.2 reflect fluctuations in the German baseline incidence data.

Baseline in the pooled cohort is not available; therefore there is no direct way to model transfer of risk from the pooled cohort to population in Germany. The LSS cohort is a major (64% on person-years) contributor to the pooled cohort, so baseline in the LSS cohort have been compared to that in Germany to estimate the range of baseline ratios. Finally, for implementation in ProZES, inherent variability of transfer factor has been modelled as defined in Chapter 5 with ratio of baselines distributed log-uniformly in the range from 1/3 to 3.

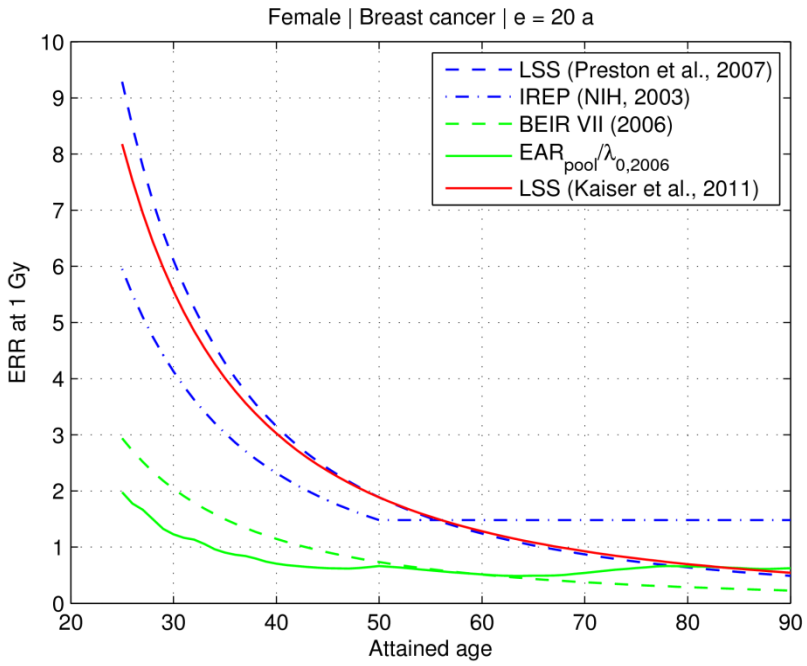

Fig. 9.1 ERR for breast cancer after exposure at age 20. For the calculation with the EAR model from the pooled study, breast cancer incidence in Germany in 2006 has been used

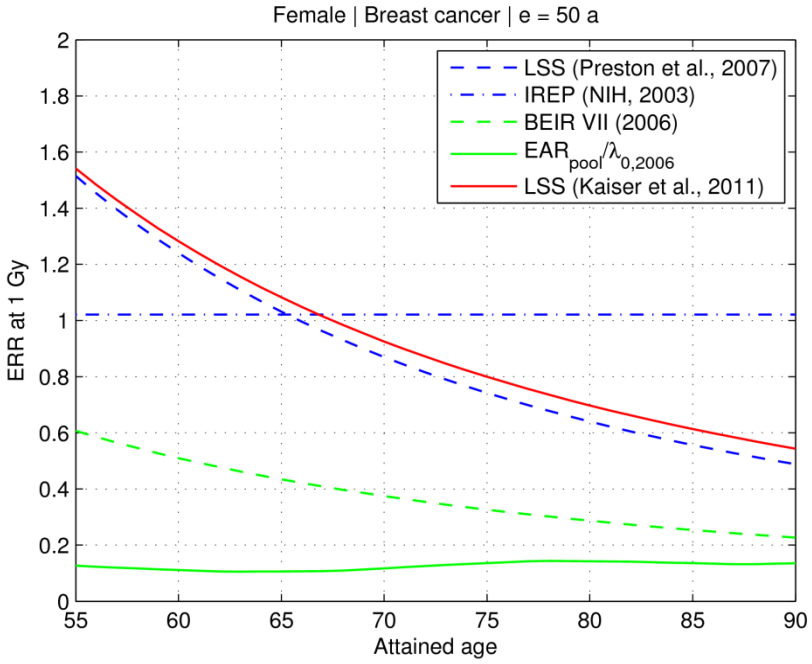

Fig. 9.2 ERR for breast cancer after exposure at age 50. For the calculation with the EAR-model from the pooled study, breast cancer incidence in Germany in 2006 has been used

Best estimates and 95% confidence intervals of breast cancer ERR for the models of Preston (2010) and Kaiser et al. (2011) are compared in Fig. 9.3 and Fig. 9.4.

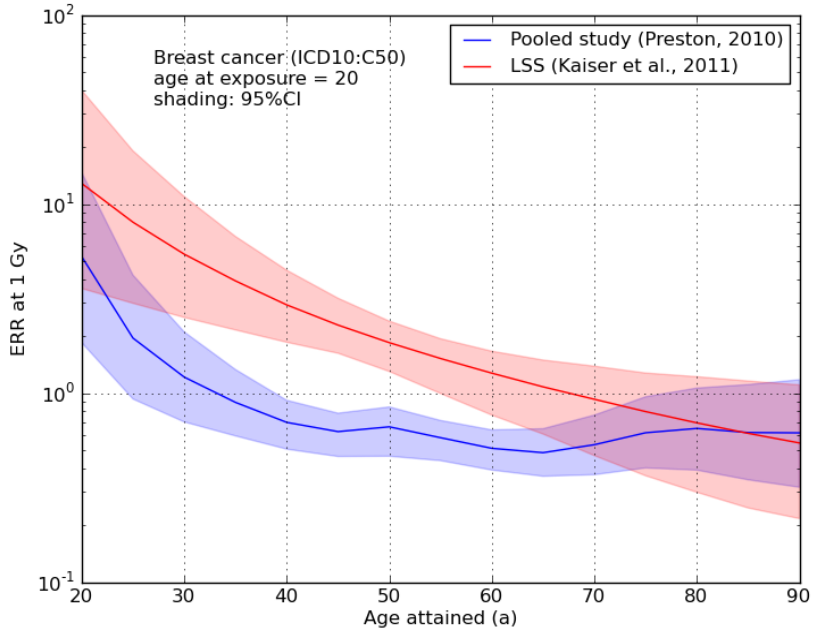

Fig. 9.3 ERR estimates and 95% confidence intervals for age at exposure 20 according to the ERR_{LSS} model of Kaiser et al. (2011) and the EAR_{pooled} model of Preston (2010). For the calculation with the EAR-model from the pooled study, breast cancer incidence in Germany in 2006 has been used

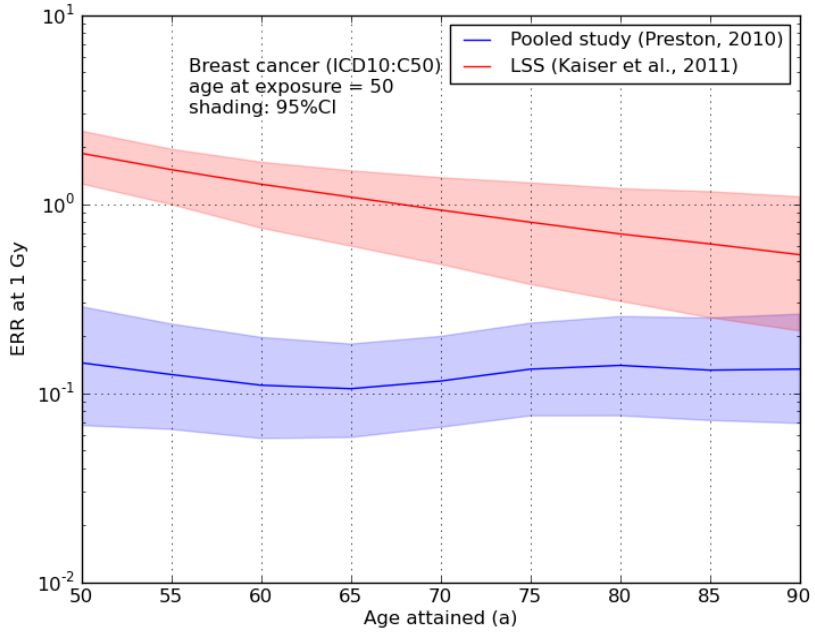

Fig. 9.4 ERR estimates and 95% confidence intervals for age at exposure 50 according to the ERR_{LSS} model of Kaiser et al. (2011) and the EAR_{pooled} model of Preston (2010). For the calculation with the EAR-model from the pooled study, breast cancer incidence in Germany in 2006 has been used

9.5. IREP/ProZES comparisons for breast cancer

9.5.1. Single exposure

Comparison of estimates made with ProZES and IREP has been performed for female breast cancer (ICD10:C50) at age 70 after exposures at ages 20 or 50 years. In ProZES, single 1-Gy-exposure has been considered with low dose rate (LDR) equal to 0.042 mGy h^{-1} and with high dose rate (HDR) larger than 6 mGy h^{-1}. Alternative estimates of assigned share made using IREP-NCI have been done for 'chronic' and 'acute' exposures, correspondingly.

Estimates of assigned share derived according to ProZES methodology are compared with results from the on-line version of IREP-NCI in Fig. 9.5. Numerical values of both techniques for 1,5,10,50,95,99%-iles are given in Table 9.2.

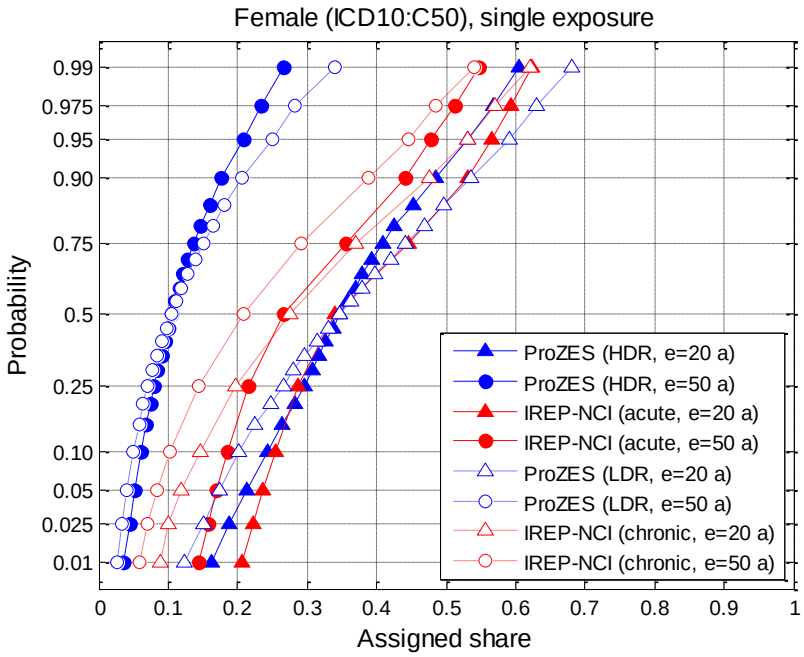

Fig. 9.5 Assigned share, Z, for breast cancer in 2006 for a female born in 1936 after exposure at ages 20 or 50 years with dose of 1 Gy (IREP – acute or chronic exposure, ProZES – exposure with high or low dose-rate)

Table 9.2 Percentiles of distributions of Z for female breast cancer at age 70 in 2006 after exposure at 1 Gy at ages 20 or 50.

Q	*e*=20 a				*e*=50 a			
	ProZES		IREP		ProZES		IREP	
	HDR	LDR	acute	chronic	HDR	LDR	acute	chronic
0.01	0.163	0.123	0.207	0.088	0.036	0.026	0.144	0.060
0.05	0.213	0.173	0.237	0.119	0.051	0.040	0.170	0.083
0.1	0.243	0.202	0.254	0.145	0.060	0.050	0.185	0.103
0.5	0.346	0.346	0.340	0.276	0.105	0.104	0.265	0.207
0.9	0.486	0.535	0.530	0.476	0.177	0.207	0.440	0.388
0.95	0.531	0.590	0.566	0.532	0.208	0.250	0.479	0.445
0.99	0.604	0.682	0.623	0.621	0.267	0.339	0.547	0.541

9.5.2. Thirty years of protracted exposure

Assigned shares for breast cancer (ICD10:C50) for 30 annual exposures at ages, starting from 20 years, with total dose of 1 Gy are compared in Fig. 9.6. ProZES estimates are done for LDR and HDR exposures, while estimates made using IREP-NCI are for both acute and chronic exposure scenarios. Numerical values for important quantiles are shown in Table 9.3.

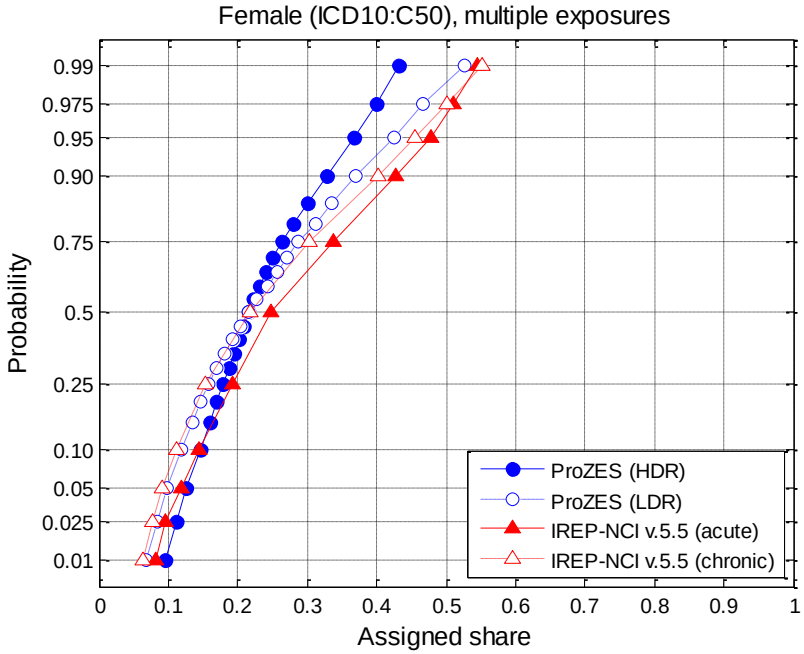

Fig. 9.6 Distribution of assigned share, Z, for breast cancer in 2006 of a female, born in 1936 after 30 exposures with total dose of 1 Gy starting at age 20 (IREP – chronic exposures, ProZES – high and low dose-rate exposures)

Table 9.3. Percentiles of distributions of Z for female breast cancer at age 70 in 2006 after 30 low dose-rate annual exposures with a total dose of 1 Gy starting at age 20.

Q	ProZES		IREP	
	HDR	LDR	acute	chronic
0.01	0.096	0.069	0.082	0.064
0.05	0.125	0.099	0.118	0.090
0.1	0.146	0.119	0.145	0.112
0.5	0.215	0.215	0.248	0.219
0.9	0.328	0.370	0.427	0.401
0.95	0.368	0.425	0.478	0.455
0.99	0.432	0.526	0.546	0.552

10. IMPLEMENTATION OF PROZES

10.1. Data and model parameters

Computations of personalized share of radiation in cancer development use the following:

- Statistical data on cancer incidence in Germany
- German demography statistics
- Parameters of the implemented cancer risk models
- Pertinent personal data (age, gender, other) and occupational exposure history for an individual under study

Sources of cancer statistics and demographical information:

- Das Zentrum für Krebsregisterdaten in Robert-Koch-Institut (RKI 2010, 2012)
- Die Gesundheitsberichterstattung des Bundes, Statistisches Bundesamt (GBE 2012)
- Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID 2012)
- Bevölkerungsbezogenes Krebsregister Bayern (BKB 2011)

Availability of the cancer statistics is shown in Table 10.1. In the nation-wide datasets (GEKID 2012, RKI 2012), statistical data are given for colorectal cancers (ICD10:C19-21), so the incidence data for colon cancer only (ICD10:C18) as found in the Cancer Register of Bavaria (BKB 2011) has been used in ProZES. Use of the Bavarian statistics for colon cancer has resulted in a narrower period of years of diagnosis: from 2002 to 2008.

Table 10.1. Availability of data on incidence of cancer types included in ProZES

ICD10 code	Cancer	Period	Source
C16	Stomach	1980–2008	RKI (2012)
		2009	GEKID (2012)
C18	Colon	2002–2008	BKB (2011)
C34	Lung	1980–2008	RKI (2012), incl. trachea cancer ICD10:C33
		2009	GEKID (2012), incl. trachea cancer ICD10:C33
C50	Breast (female only)	1980–2008	RKI (2012)
		2009	GEKID (2012)

Model parameters used in the implemented risk models have been described in details above, in Chapters 6–9.

Person-specific data include:

- ✓ Gender
- ✓ Birthyear
- ✓ Year of diagnosis
- ✓ Diagnosis (in ICD10 classification)
- ✓ Personal exposure history as a series of exposure events specified by month and year of start, duration (in working hours), radiation type (currently only low-LET radiation with RBE=1), radiation dose distribution with parameters (supported are uniform “U”, triangle “T”, normal “N”, and log-normal “LN”)

A user of the ProZES program can use provided templates to create input files with person-specific information. ProZES supports input and output using common Microsoft Excel-specific formats for the input data: *.xls and *.xlsx. Alternatively, comma-separated (*.csv) and tab-delimited (*.txt) formats are available both for input and output. The user can also create or edit the person-specific data directly in the ProZES program and save these for later use.

10.2. Algorithm

Inherent uncertainties of estimates of radiation risk imply that not only best estimates but also distribution of assigned share is important to account for in decision-making process. Propagation of errors of radiation risk models, their combination with effects of various stochastic factors can be done by sampling using Monte Carlo method (method of random trials).

Main simulation cycle starts after the ProZES user has loaded or prepared input data and pressed "ProZESsieren!" button. The main execution steps are outlined below:

→ Check/verify input data:
- Personal data (gender *s*, birthyear *by*, year of diagnose *cy*, cancer type *c*)
- Details of previous radiation exposure (year, radiation type, duration in working hours, parameters of the dose distribution)

→ Specify:
- Origin of the cancer risk model: LSS, non-LSS
- Type of risk transfer: additive, multiplicative, ProZES (both)

→ Prepare and output the report header: summary of the input parameters

→ Get the cancer incidence rate $\lambda_0(cy)$ and population size $N_0(cy)$ in Germany in year *cy*

→ Build a list of models for the cancer *c*:
- Model *M1* with AIC-weight ω_1
- Model *M2* with AIC-weight ω_2
- …
- Model *MN* with AIC-weight ω_N

→ Start the main cycle (generation of distribution of Z)
- compute additional uncertainty factor to express uncertainties related to the LSS dosimetry:
  - $F_{LSS} = F_d F_{n-RBE}$ for LSS-based models (see Section 4.1)
  - $E_{LSS} = 1$ for all other models
- Sample parameters t_0 and τ for the function describing latency period (see eq. (4.2))
- Sample risk transfer factor *f* (see eq. (5.4))
- Sample percentile for DREF (see Section 4.3)
- Select the model *Mm* to be used in the given iteration (randomly sample accordingly to AIC-weight)
- Re-sample incidence rate in Germany for the given cancer, gender, and age group, assuming Poisson distribution for the number of registered cancer cases
- Start cycle over the list of exposures
  - Sample dose *d** from the given dose distribution
  - Compute latency correction factor F_L
  - Compute and apply correction factor F_{RBE} accounting for RBE of the given radiation type (presently, low-LET radiations only, i.e. F_{RBE}=1)
  - Compute GSD of DREF for the given dose rate (see eq. (4.4))

- Compute DREF for the pre-sampled percentile
- For the selected model *Mm* sample parameters and compute model baseline and excess incidence rates: $\lambda_{0,m}$ and h_m
- Compute excess relative risk and transfer it to the target population

$$ERR = \frac{h_m}{\lambda_{0,m}}\left(1 - f + f\frac{\lambda_{0,m}}{\lambda_0}\right)$$

- Apply correction and modifying factors: $ERR \leftarrow ERRF_L F_{LSS}/DREF$
- Compute $Z = ERR/(1 + ERR)$

→ Compute percentiles of generated distributions *ERR* and *Z*
→ Return from computational routine to the main program
→ Plot distribution of Z
→ Finalize and display output report

10.3. Implementation

Programmatically, ProZES is a Windows application with graphical user interface (GUI) (see Fig. 10.1). Technically, the program can be described as a Windows Presentation Foundation (WPF) application built on the top of .NET Framework (version 4 and higher). Use of WPF toolkit allows for modern-looking, feature-rich and user-friendly application. The program is distributed as SingleClick application, which means fully automated installation with checks for necessary pre-requisites, e.g. existence on the user computer of appropriate version of the .NET Framework. If some pre-requisites are missing, then the installation routine automatically downloads and installs them.

Although important, user-friendliness was not the only requirement to the program. Another essential property of the program being developed was its computational performance. Because of selection of Monte Carlo techniques for simulation and generation of probability distributions, the stochastic modelling and numerical computations have been isolated into a separate dynamically-linked library. This library has been built using Intel's Fortran compiler and Math Kernel Library (at the time of writing of versions XE2013.1 and 11.0, correspondingly). Combination of .NET-based (a.k.a. "managed") code and statically-compiled ("unmanaged") highly-optimized numerical routines from Intel MKL has allowed to meet the both criteria, i.e. computational effectiveness and user-friendliness and simplicity of use.

The following Figs 10.1–10.3 illustrate the outlook of the ProZES program, show input options, and two possibilities of output: graphical (Fig. 10.1) and textual (Fig. 10.2).

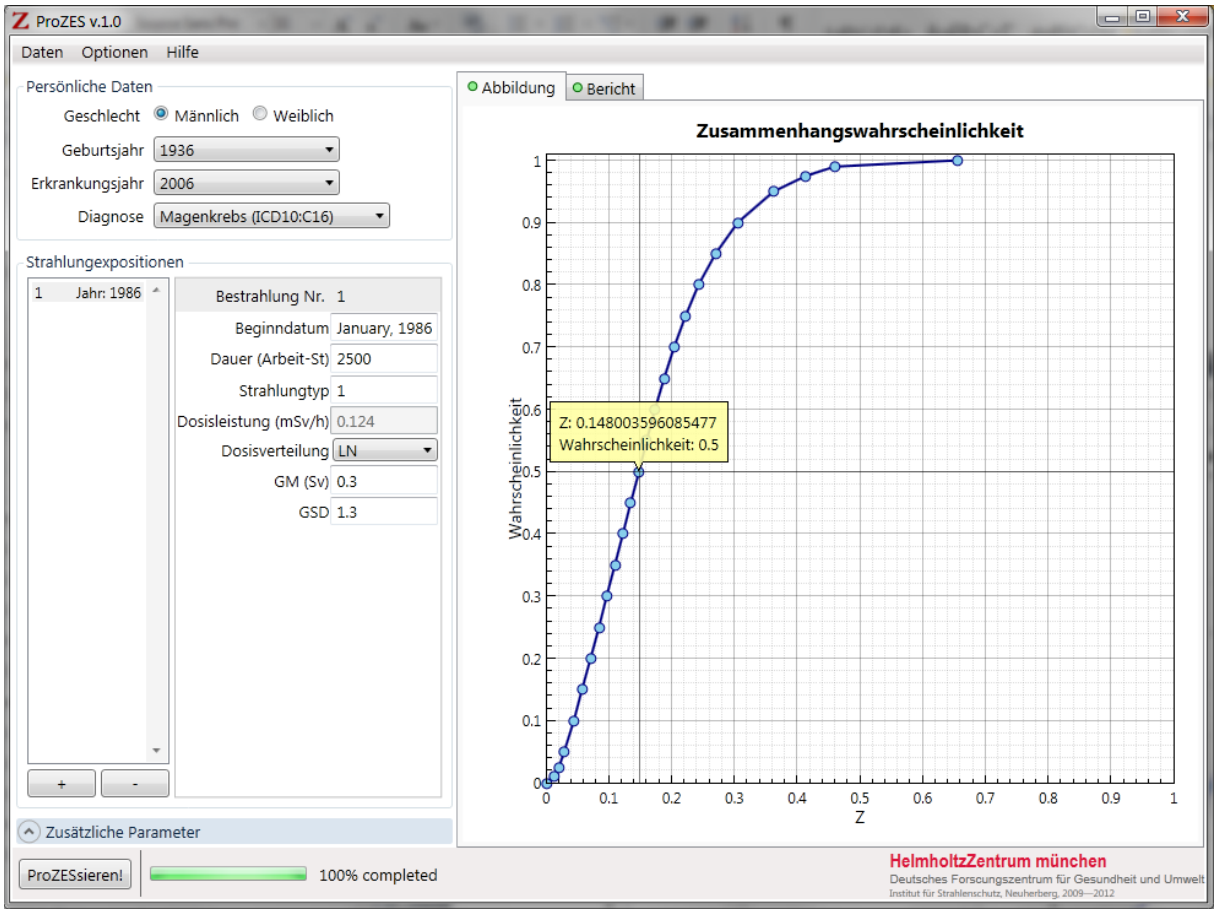

Fig. 10.1. Screenshot of the ProZES program with graphic output window

The program provides possibility to input person-specific data either manually or load them from an external file. The various formats are supported, including Microsoft Excel (*.xls, *.xlsx), comma- and tab-separated (*.csv, *.prn) files. The user can save modified input parameters in files using the same formats.

Sample size in stochastic simulations can be varied in the range from 10 to 50000 trials (Monte Carlo histories). Correspondingly, preliminary calculations in complex cases, with extensive exposure history, can be run at reduced sample sizes, while for the final estimates the sample size can be increased. The recommended range spans from 3000 to 15000.

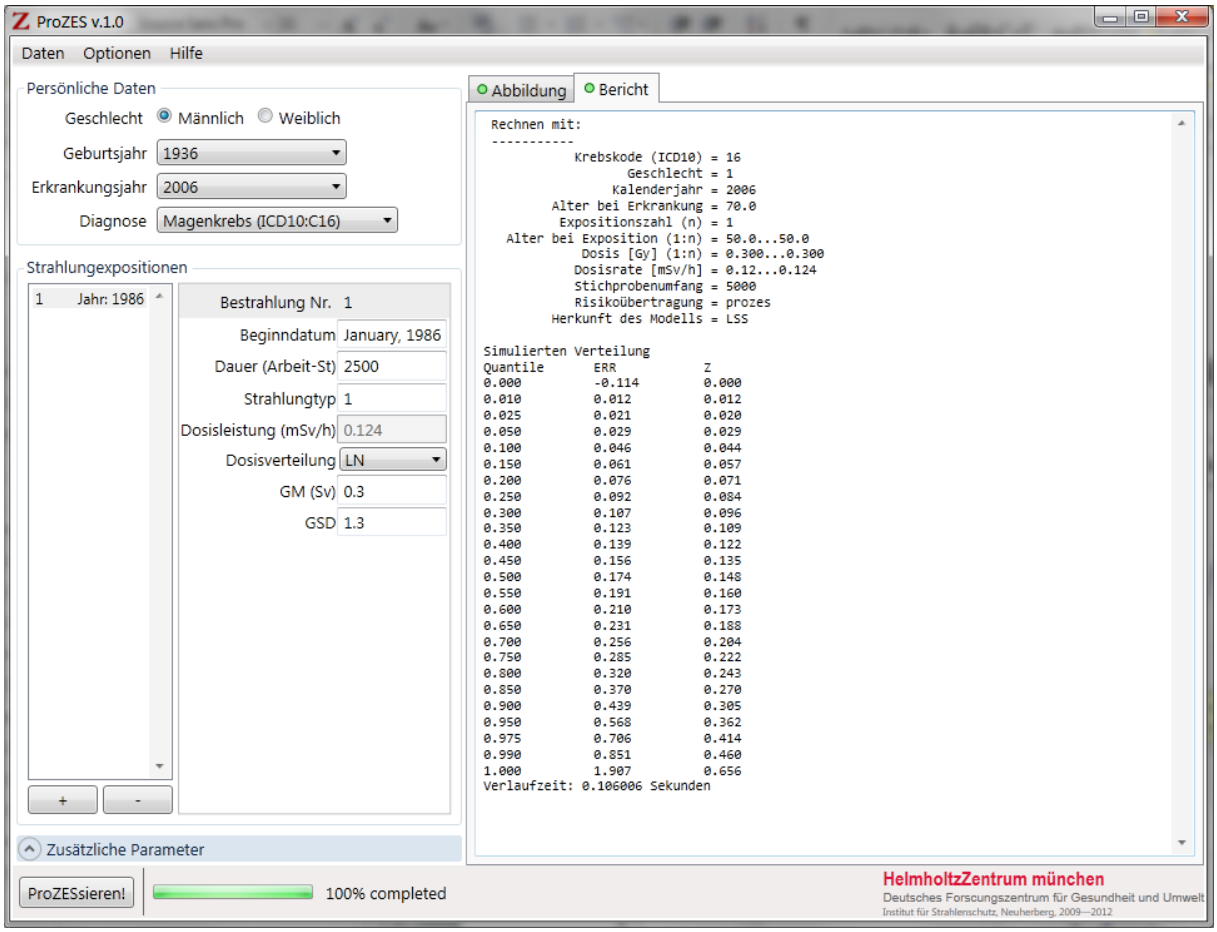

Fig. 10.2. Screenshot of the ProZES program with textual output window

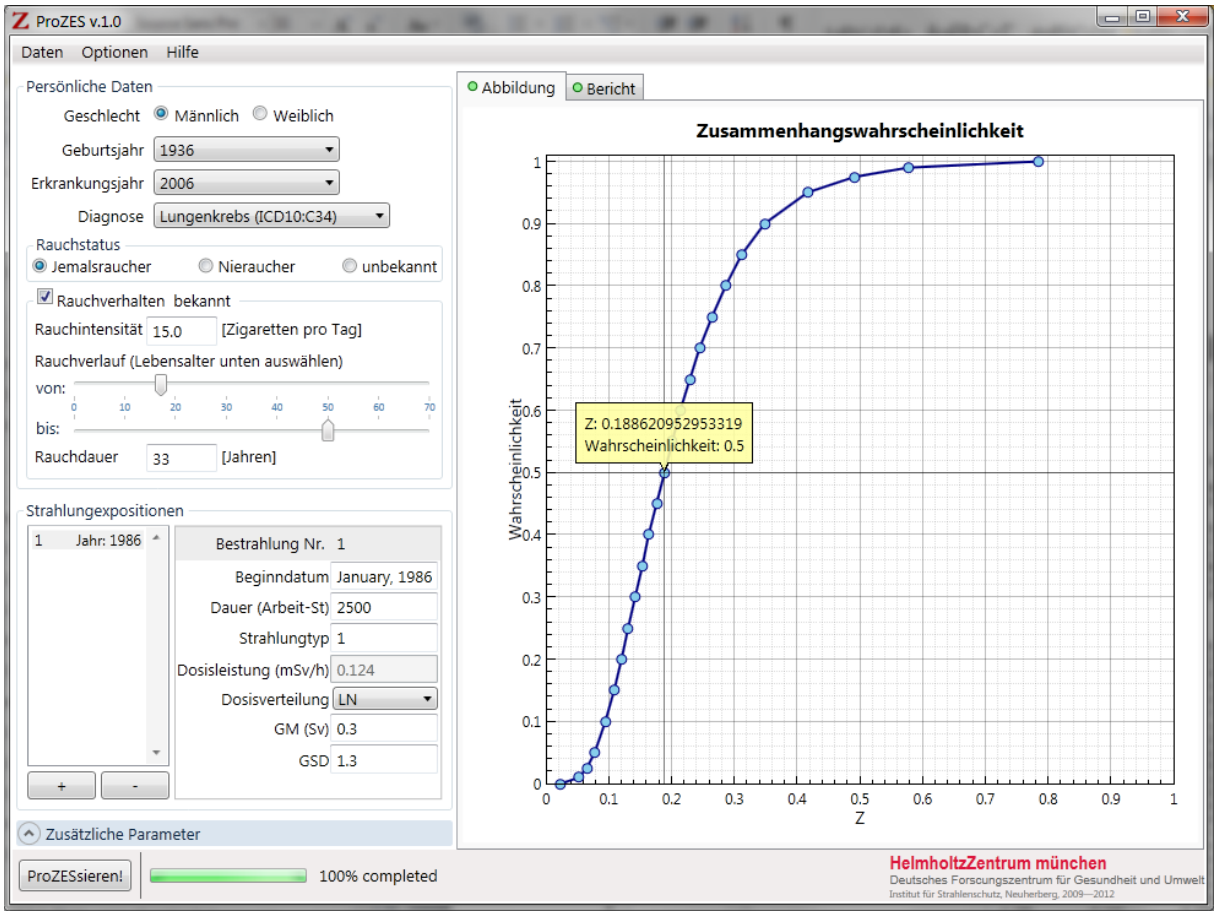

Fig. 10.3. Screenshot of the ProZES program showing controls for input of smoking-specific personal information.

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