Bundesamt
für Strahlenschutz

Anlage 1

zum Ressortforschungsbericht zum Strahlenschutz

Erweiterung und Aktualisierung von ProZES

Abschätzung der Zusammenhangswahrscheinlichkeit bei Erkrankungen an mehreren Primärtumoren

Vorhaben 3618S72230

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Erweiterung und Aktualisierung von ProZES

(Programm zur Berechnung der Zusammenhangswahrscheinlichkeit zwischen einer Erkrankung und einer Strahlenexposition)

Vorhaben 3618S72230

Anhang 1

Abschätzung der Zusammenhangswahrscheinlichkeit bei Erkrankungen an mehreren Primärtumoren

(auf Englisch)

Assessment of the assigned share in case of more than one primary cancer

(in English)

ASSESSMENT OF THE ASSIGNED SHARE IN CASE OF MORE THAN ONE PRIMARY CANCER

ProZES provides the functionality to calculate the assigned share (Zusammenhangswahrscheinlichkeit Z) that at least one out of several primary cancers was caused by radiation exposure. This assigned share is larger than the assigned share of each individual cancer. This appendix describes and discusses the methodology to calculate the assigned share for two or more primary cancers, as implemented in ProZES. First, the formulas are derived for fixed values of assigned shares without uncertainties. Then, assigned shares with uncertainty distributions are discussed including results from numerical simulations. Finally, the results are compared to IREP and summarized.

1 FIXED VALUES OF ASSIGNED SHARES WITHOUT UNCERTAINTIES

In the following it is assumed that development of the observed cancers can be regarded as independent. Due to the stochastic nature of cancer induction by radiation, and the fact that only primary cancers are considered, in general this assumption should be well fulfilled. However, dependencies are possible if, e.g., treatment of the first cancer has induced or accelerated another cancer. In this case the calculation of Z according to the formula implemented in ProZES, assuming cancer independence, will give a higher value for Z than a calculation assuming partial dependence.

Let X_i indicate whether primary cancer *i* is radiation-induced ($X_i = 1$) or not ($X_i = 0$). It is assumed that the X_i are independent. Z_i is the probability that primary cancer *i* was caused by radiation. The product $\prod_i (1\text{-}Z_i)$ is the probability that no cancer was induced by radiation. Therefore,

$$\boldsymbol{Z_{total} = 1 - (1 - Z_1)(1 - Z_2)} \quad \textbf{(1)}$$

$$\boldsymbol{Z_{total} = 1 - \prod_i (1 - Z_i)} \quad \textbf{(2)}$$

gives the total assigned share that radiation has induced at least one cancer in the case of two primary cancers, and of multiple primary cancers, respectively.

2 ASSIGNED SHARES WITH UNCERTAINTY DISTRIBUTION

Assessment of the assigned share is necessarily connected with uncertainties from different sources, e. g. from the assumed doses or the risk models. Each Z_i has an uncertainty distribution with corresponding percentiles Z_i^p, where *p* represents the percentile. For example, *p*=50 corresponds to the median, *p*=16 and *p*=84 to 1σ errors for a normal distribution. With regard to the uncertainties from the various sources, the different Z_i's can be mutually uncorrelated, partially correlated or fully correlated.

A selected percentile p may be approximated by the same formula, using the corresponding percentile of the individual Z_i's:

$$\boldsymbol{Z_{total}^{(p)} = 1 - \prod_i \left(1 - Z_i^{(p)}\right).} \quad \textbf{(3)}$$

This formula is exact in the case of fully correlated $Z_i's$, since full correlation implies that if a certain percentile *p* of $Z_1^{(p)}$ is selected, also the same percentile $Z_2^{(p)}$ is chosen (and similarly for multiple cancers). As discussed in detail below, the formula usefully approximates the real case also for partially correlated or fully uncorrelated $Z_i's$.

In practice, it is virtually impossible to determine the degree of correlation. The uncertainties arise from different sources, e.g. from organ doses, model uncertainties, DREF factor, transfer from the Japanese to the German population etc. Each uncertainty can be more or less correlated among different cancers. In general, a realistic case will therefore be located in-between the fully correlated and the uncorrelated cases.

3 NUMERICAL ANALYSIS OF THE DEGREE OF APPROXIMATION BY FORMULA (3)

To validate how well equation (3) approximates the total assigned share in the case of partially correlated or uncorrelated assigned shares for multiple primary cancers, numerical simulations were performed for two primary cancers with Z_1 and Z_2. First, uncorrelated, partially or fully correlated pairs (Z_1, Z_2) from the Z_1, Z_2 distributions were sampled repeatedly. Then various percentiles *p* of Z_{total} were calculated in two different ways:

1. Simulation of 'true' $Z_{total}^{(p)}$
   by generating the distribution for Z_{total} via $Z_{total} = 1 - (1 - Z_1)(1 - Z_2)$, and then by determining the percentiles of Z_{total}(simulation result); or
2. Approximation of $Z_{total}^{(p)}$
   by calculating the percentiles *p* for the Z_1 and Z_2 distributions, and then applying $Z_{total}^{(p)} = 1 - (1 - Z_1^{(p)})(1 - Z_2^{(p)})$.

The simulations were performed in Matlab (The Mathworks Inc., USA) using N=10,000 pseudo-random pairs $(Z_1^{(p)}, Z_2^{(p)})$ from normally and log-normally distributed Z_1, Z_2. Eighteen scenarios were studied in which the correlation of Z_1 and Z_2, their mean values and standard deviations were varied. Especially for wide distributions, some of the generated pseudo-random values fell outside the interval [0,1], so that they could not represent probabilities of causation; such values were discarded.

The distributions Z_{total} resulting from the two approaches are compared in Table 1. As illustrated by these results, formula (3) is exact for the fully correlated case (scenario 5). For the general case of partially correlated distributions and even for fully uncorrelated distributions, the median (which is a main concern in ProZES) is very well represented by formula (3) (boldface entries in the last column of Table 1). The largest difference between the median from the simulation and formula (3) was found in scenario 18, with asymmetric distributions and large uncertainties. However, even in this case the difference was only about 10%, with 0.46 vs. 0.52.

The differences between both approaches become larger for other percentiles, and are largest for very low or very high percentiles. As a general feature, formula (3) predicts for partially correlated assigned shares a larger uncertainty interval than the realistic simulations. In scenario 2 for two normal distributions with mean of 0.3 and standard deviation of 0.1, the 99th percentile $Z_{total}^{(99\%)}$ is 0.78 from formula (3), but 0.72 for the simulation, whereas the median values are almost identical. These deviations are largest for the uncorrelated case, and decrease with increasing correlation between Z_1 and Z_2 (scenarios 2–5 or 14–15). Furthermore, the deviations increase with increasing individual uncertainties (i.e., distribution widths) of Z_1 and Z_2 (scenarios 1-2 + 6-7, or 16-18).

The resulting assigned share for the case of two primary cancers is illustrated in Figure 1. To reach a total assigned share above 50% (green line), it is for instance sufficient to have two cancer cases with 30% assigned share each, but not one with 20% and another one with 30% or even 35%.

4 ASSIGNED SHARE FOR MULTIPLE PRIMARY CANCERS IN NIOSH-IREP

For the purpose of adjudicating claims for compensation in the U.S., the NIOSH-IREP tool works with the upper 99% credibility limit of Z (denoted there as PC/AS for probability of causation/assigned share), i.e. with the 99th percentile of the corresponding probability distribution of Z. For multiple primary cancers, first the NIOSH-IREP code is run for each primary cancer separately to obtain the upper 99% credibility limit $Z_i^{(99\%)}$ for these cancers. Then the upper 99% credibility limit of Z_{total} for all cancers combined is calculated by Kocher et al. (2008):

$$Z_{total}^{(99\%)} = 1 - \prod_i (1 - Z_i^{(99\%)}). \quad \textbf{(4)}$$

This formula is identical to the formula (3) implemented in ProZES. In Kocher et al. (2008) it was commented that by the use of this formula all uncertain Z_i are assumed to be perfectly correlated, and that the resulting $Z_{total}^{(99\%)}$ is higher, and thus more favorable to claimants, than the upper 99% credibility limit that would be calculated by assuming that all Z_i are uncorrelated. This is supported by the simulation study provided in this document.

5 CONCLUSION

Based on the simulations, formula (3) is applied in ProZES similarly to NIOSH-IREP. The user should run ProZES independently for each primary cancer. The specific percentile *p* of the total assigned share $Z_{total}^{(p)}$ can then be calculated by providing the software with the values $Z_i^{(p)}$ of the percentile *p* of the different cancers.

The use of formula (3) in ProZES for multiple primary cancers is well justified: It provides a good approximation for the median of the assigned share that is of main interest in ProZES. In addition, the actual uncertainty of the assigned share is smaller than the predicted one, so that upper percentiles calculated in ProZES are larger than the actual ones for a partially correlated case.

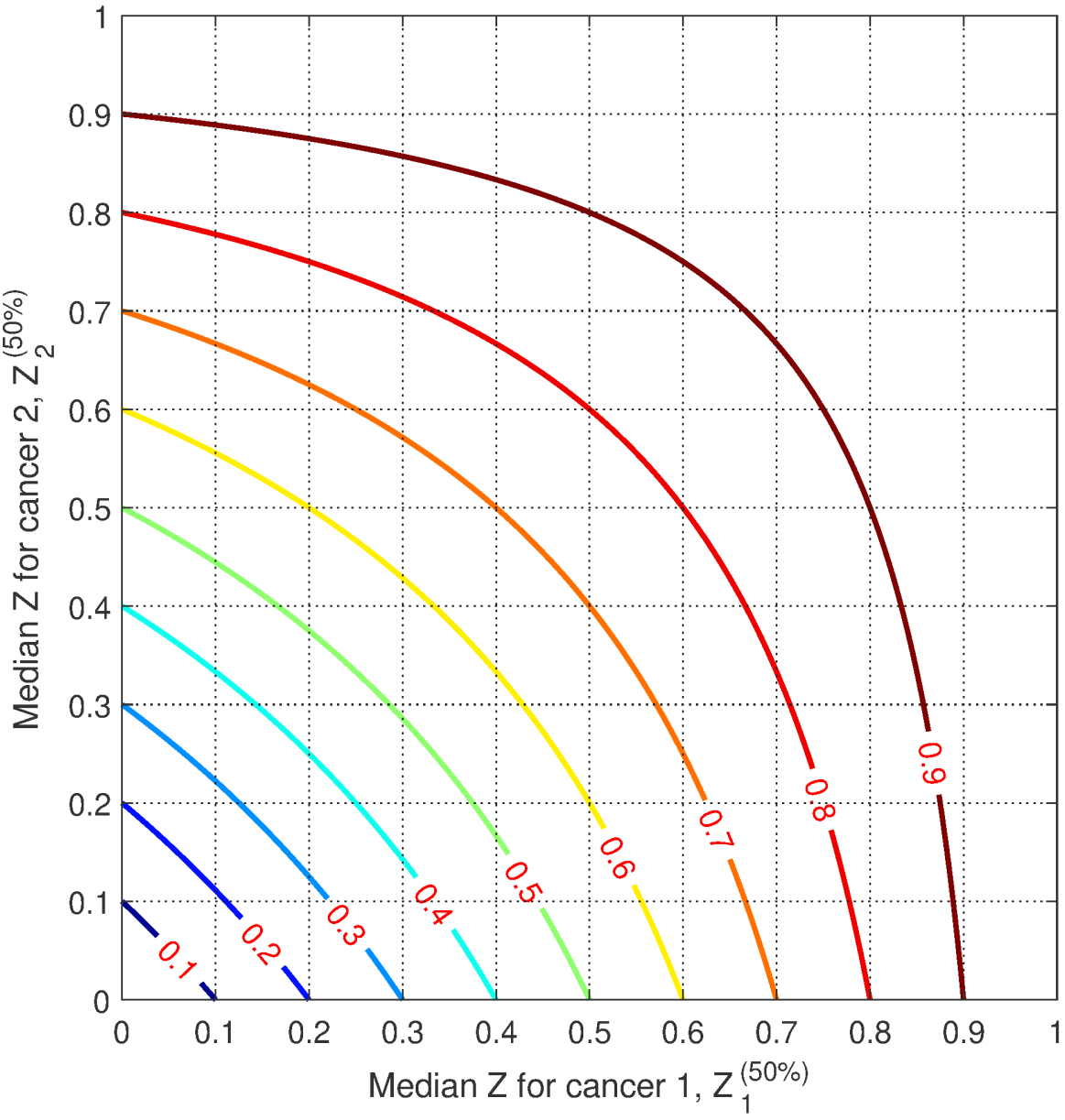
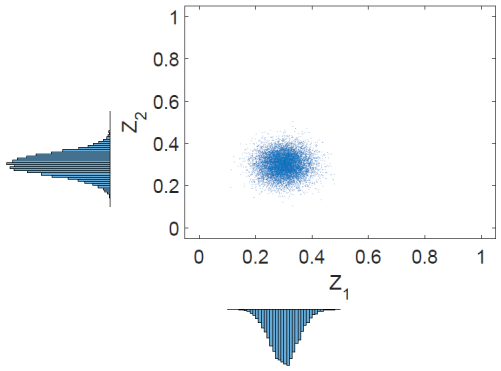
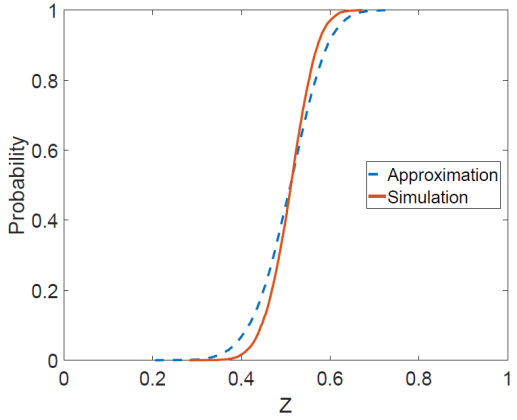
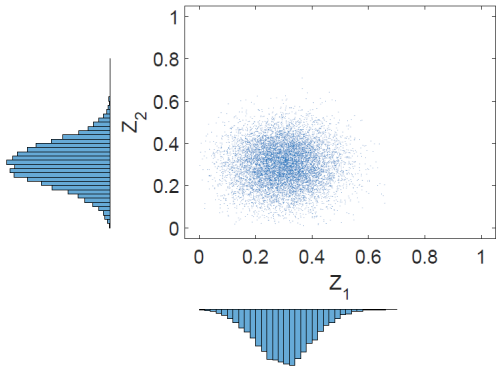
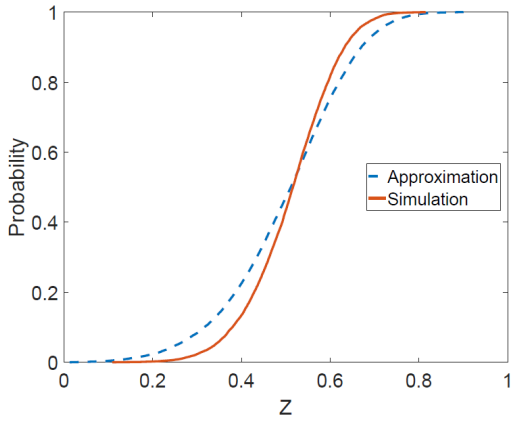
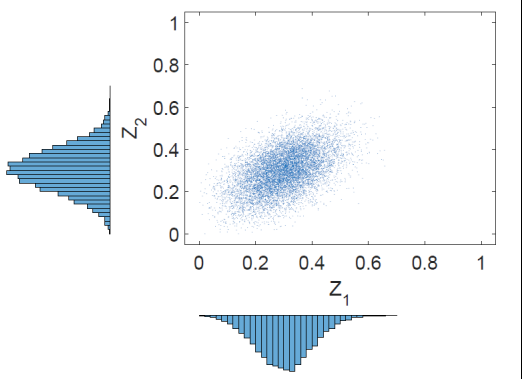
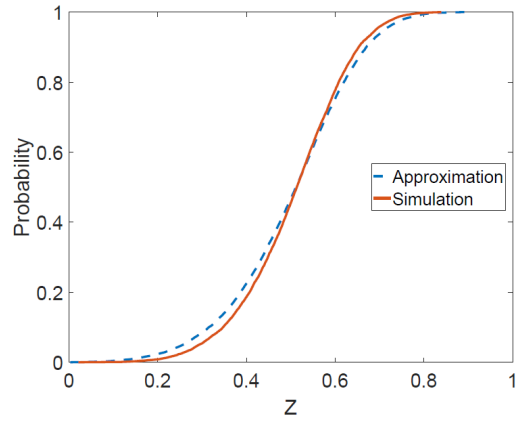
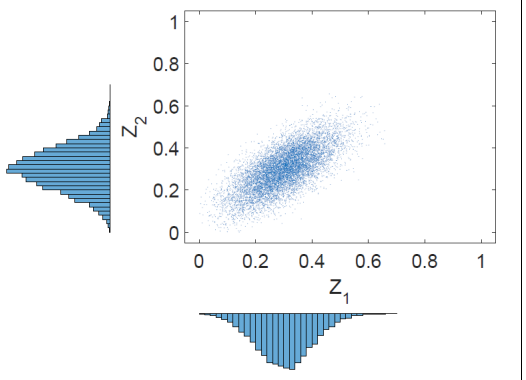
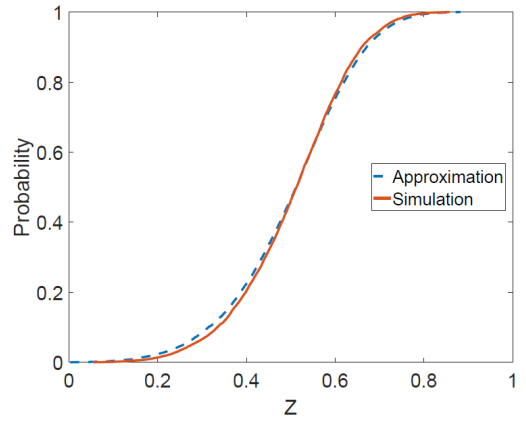
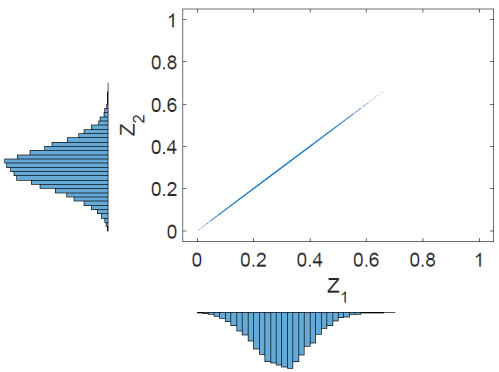
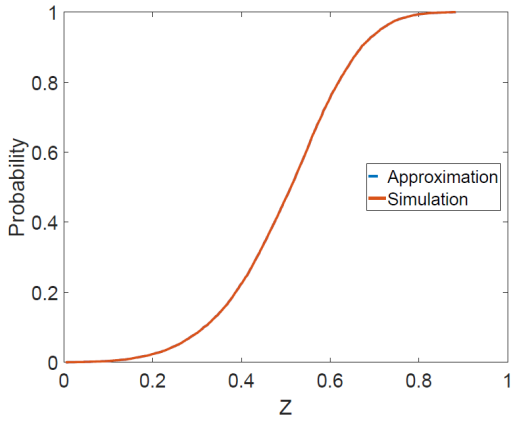
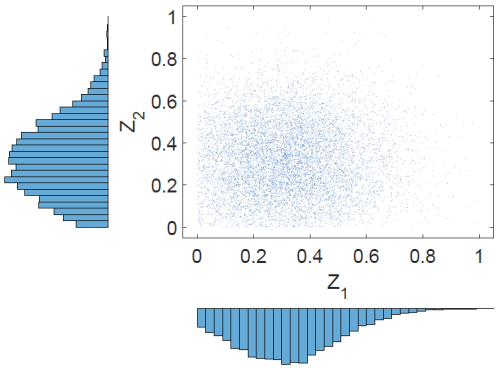
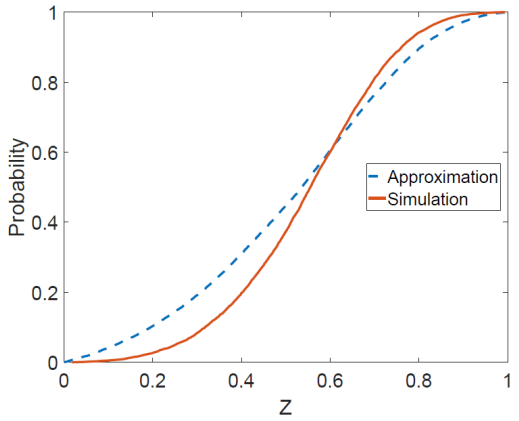


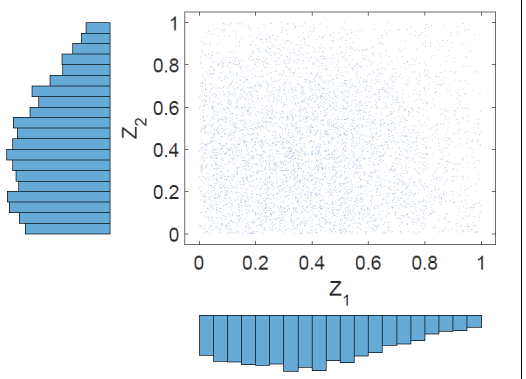
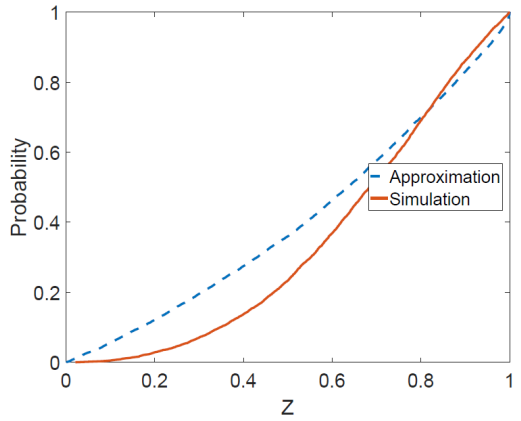
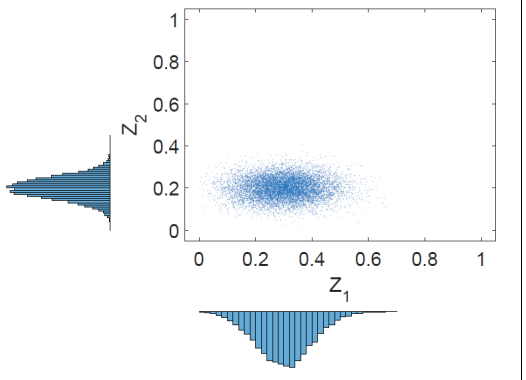
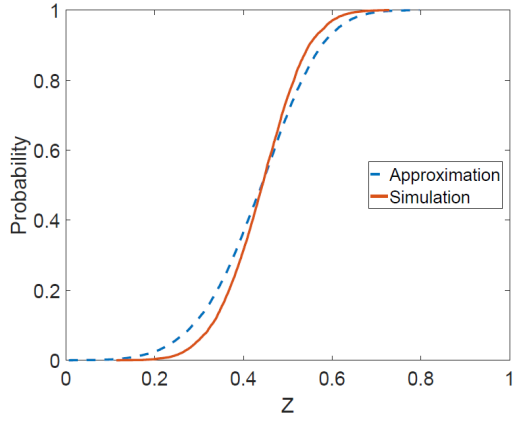
Figure 1: Median of assigned share Z_{total} that at least one of two cancers is caused by radiation, in dependence on the median of the assigned shares for these two cancers separately. For instance, for $Z_1^{(50\%)} = Z_2^{(50\%)} = 0.3$, the combined $Z_{total}^{(50\%)} > 0.5$, so it is more likely than not that one or both cancers are radiation-induced. For $Z_1^{(50\%)} = 0.3$ and $Z_2^{(50\%)} = 0.2$, $Z_{total}^{(50\%)} < 0.5$, so the median probability is less than 0.5.

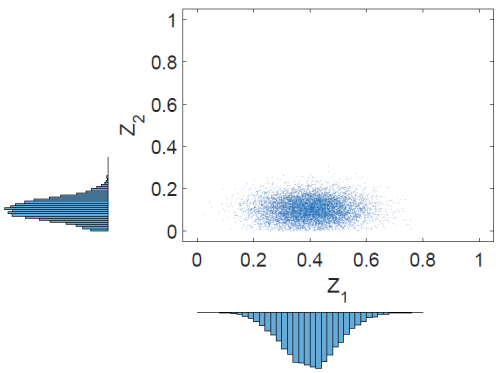
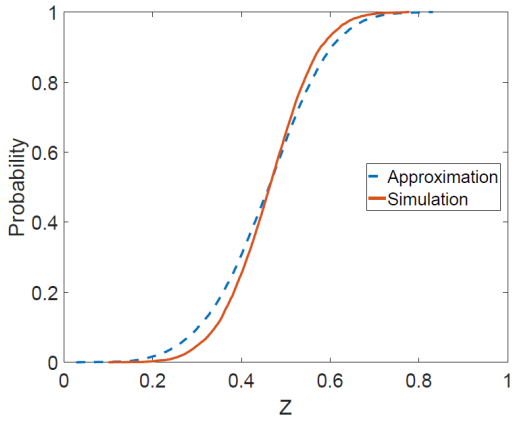
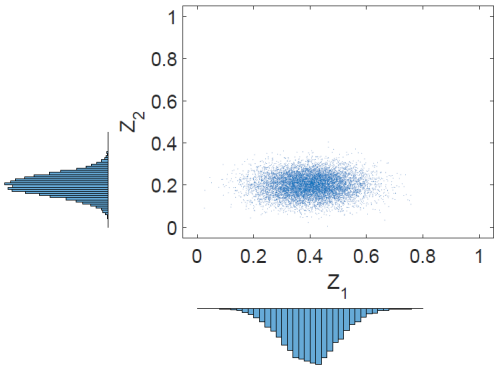
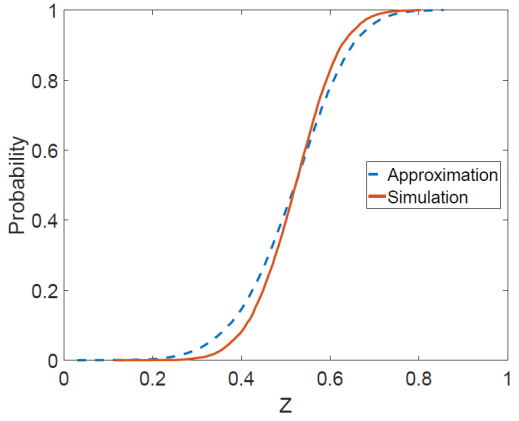
Table 1: Summary of simulation results. For alternative distributions of Z_1 and Z_2 (generating distribution: normal or log-normal, all with cut-offs at 0 and 1; mean and standard deviation listed in columns 2-3) and their correlation (column 4), shown are scatter histograms depicting Z_1, Z_2 and their correlation (column 5), comparison of Z_{total} from full simulation (with 10000 random samples) vs. approximation by the formula (3) (column 6), and numerical values for percentiles 1, 16, 50 (median, of central interest in ProZES), 84 and 99 calculated by the approximation vs. full simulation (column 7-9).

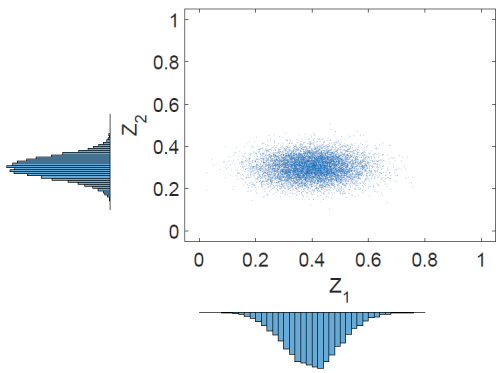
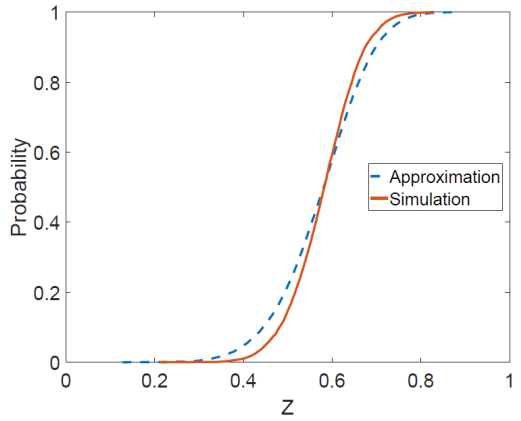
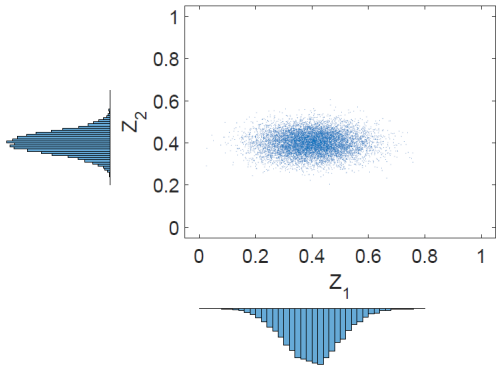
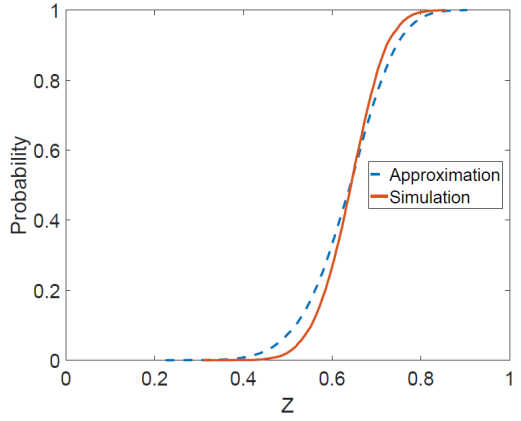
Scenario	Z_1 distr. Mean Std. dev.	Z_2 distr. Mean Std. dev.	Correl. coeff. Z_1, Z_2	Scatter-histogram	Approximation (formula) vs. simulation	Percentile %	Approx.	Sim.
1	Normal μ=0.3 σ=0.05	Normal μ=0.3 σ=0.05	0.0			1 16 **50** 84 99	0.3372 0.4387 **0.5106** 0.5764 0.6587	0.3915 0.4610 **0.5115** 0.5587 0.6186
2	Normal μ=0.3 σ=0.1	Normal μ=0.3 σ=0.1	0.0			1 16 **50** 84 99	0.1447 0.3629 **0.5113** 0.6382 0.7805	0.2639 0.4122 **0.5161** 0.6074 0.7170

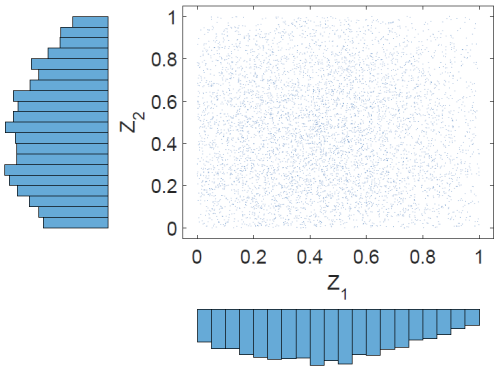
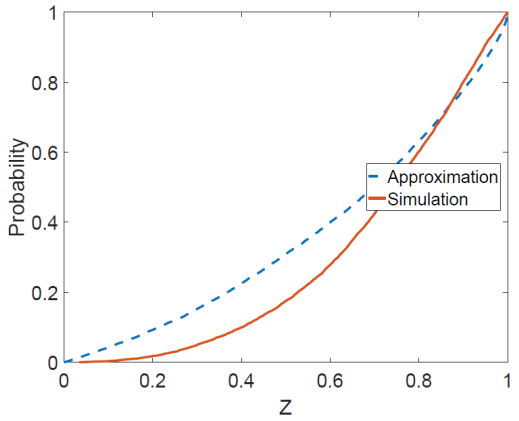
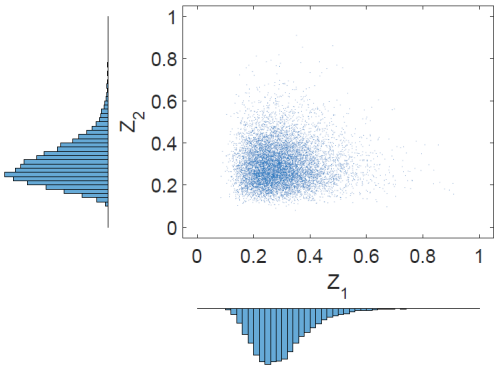
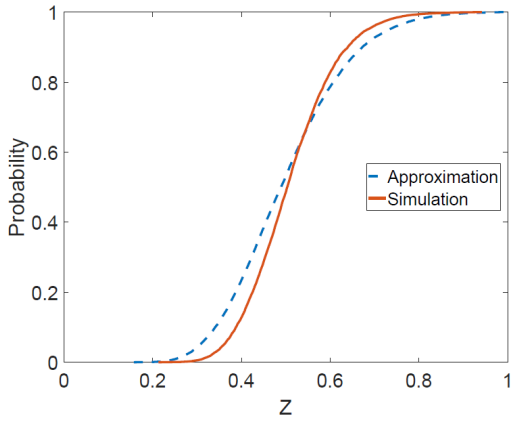
3	Normal μ=0.3 σ=0.1	Normal μ=0.3 σ=0.1	0.5			1 16 **50** 84 99	0.1462 0.3636 **0.5116** 0.6380 0.7831	0.2076 0.3855 **0.5135** 0.6243 0.7529
4	Normal μ=0.3 σ=0.1	Normal μ=0.3 σ=0.1	0.7			1 16 **50** 84 99	0.1489 0.3634 **0.5115** 0.6385 0.7821	0.1860 0.3757 **0.5129** 0.6290 0.7650

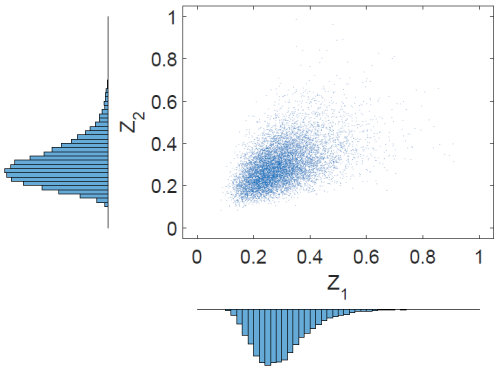
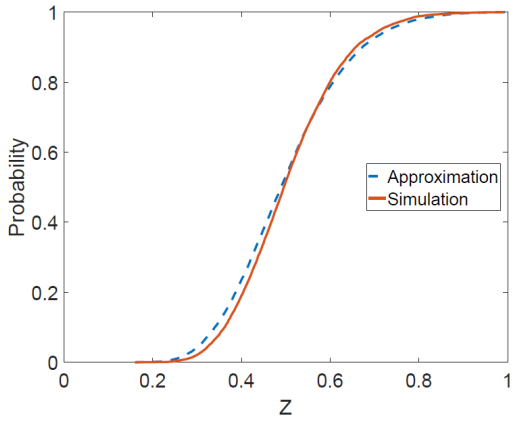
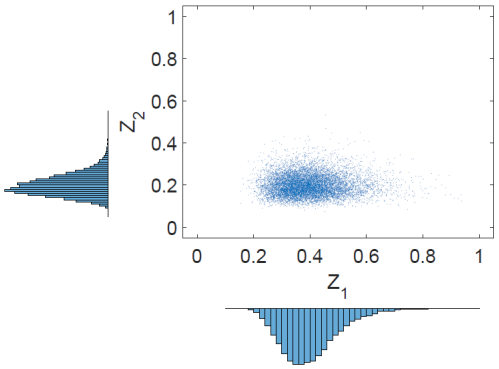
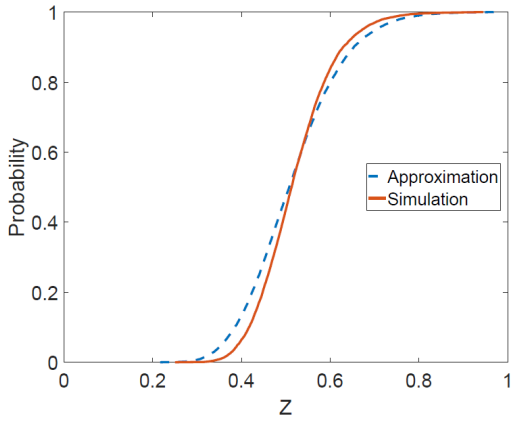
5	Normal μ=0.3 σ=0.1	Normal μ=0.3 σ=0.1	1.0			1 16 **50** 84 99	0.1501 0.3635 **0.5114** 0.6380 0.7846	0.1501 0.3635 **0.5114** 0.6380 0.7846
6	Normal μ=0.3 σ=0.2	Normal μ=0.3 σ=0.2	0.0			1 16 **50** 84 99	0.0282 0.2682 **0.5357** 0.7546 0.9453	0.1374 0.3723 **0.5554** 0.7171 0.8925

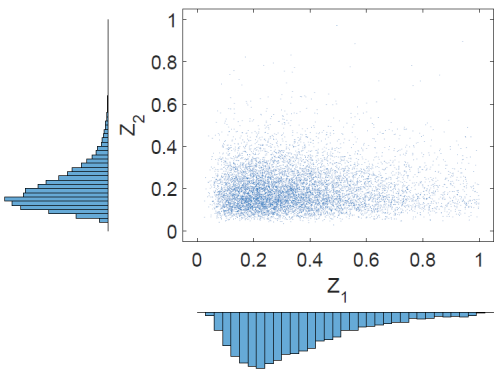
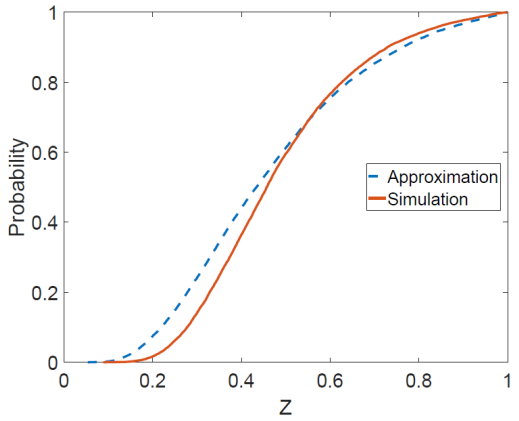
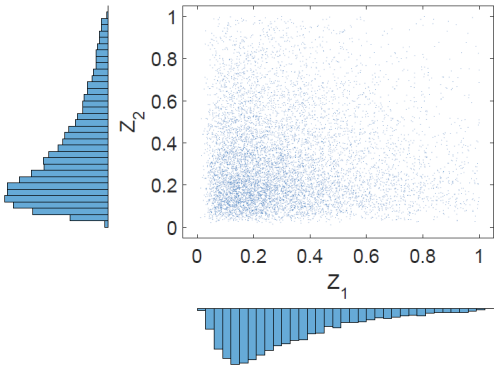
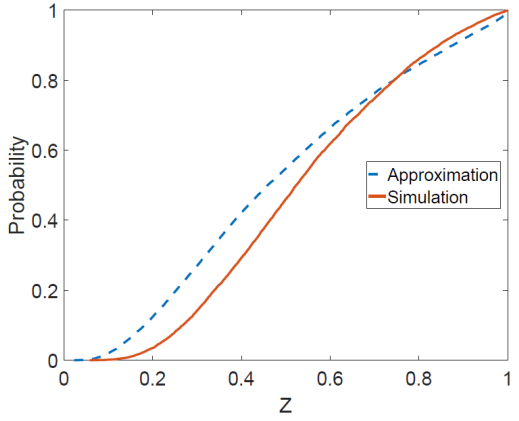
7	Normal μ=0.3 σ=0.4	Normal μ=0.3 σ=0.4	0.0			1 16 **50** 84 99	0.0190 0.2522 **0.6351** 0.9069 0.9989	0.1268 0.4279 **0.6844** 0.8867 0.9932
8	Normal μ=0.3 σ=0.1	Normal μ=0.2 σ=0.05	0.0			1 16 **50** 84 99	0.1558 0.3223 **0.4410** 0.5483 0.6815	0.2366 0.3537 **0.4427** 0.5253 0.6358

9	Normal μ=0.4 σ=0.1	Normal μ=0.1 σ=0.05	0.0			1 16 **50** 84 99	0.1815 0.3396 **0.4618** 0.5728 0.7134	0.2428 0.3681 **0.4633** 0.5536 0.6777
10	Normal μ=0.4 σ=0.1	Normal μ=0.2 σ=0.05	0.0			1 16 **50** 84 99	0.2444 0.4071 **0.5209** 0.6233 0.7501	0.3187 0.4351 **0.5220** 0.6035 0.7141

11	Normal μ=0.4 σ=0.1	Normal μ=0.3 σ=0.05	0.0			1 16 **50** 84 99	0.3269 0.4769 **0.5808** 0.6734 0.7865	0.3991 0.5044 **0.5823** 0.6545 0.7508
12	Normal μ=0.4 σ=0.1	Normal μ=0.4 σ=0.05	0.0			1 16 **50** 84 99	0.4094 0.5467 **0.6407** 0.7236 0.8229	0.4773 0.5734 **0.6426** 0.7053 0.7883

13	Normal μ=0.4 σ=0.4	Normal μ=0.4 σ=0.4	0.0			1 16 **50** 84 99	0.0257 0.3112 **0.6974** 0.9371 0.9993	0.1579 0.4840 **0.7444** 0.9196 0.9943
14	Log-normal μ=0.3 σ=0.1	Log-normal μ=0.3 σ=0.1	0.0			1 16 **50** 84 99	0.2529 0.3709 **0.4893** 0.6299 0.8428	0.3133 0.4112 **0.5033** 0.6056 0.7719

15	Log-normal μ=0.3 σ=0.1	Log-normal μ=0.3 σ=0.1	0.5			1 16 **50** 84 99	0.2525 0.3707 **0.4893** 0.6299 0.8467	0.2790 0.3885 **0.4955** 0.6188 0.8119
16	Log-normal μ=0.4 σ=0.1	Log-normal μ=0.2 σ=0.05	0.0			1 16 **50** 84 99	0.3082 0.4106 **0.5077** 0.6193 0.7977	0.3542 0.4367 **0.5131** 0.6007 0.7567

17	Log-normal μ=0.4 σ=0.3	Log-normal μ=0.2 σ=0.1	0.0			1 16 **50** 84 99	0.1269 0.2566 **0.4339** 0.6846 0.9710	0.1862 0.3094 **0.4569** 0.6621 0.9540
18	Log-normal μ=0.4 σ=0.4	Log-normal μ=0.4 σ=0.4	0.0			1 16 **50** 84 99	0.0817 0.2266 **0.4590** 0.7939 0.9958	0.1492 0.3127 **0.5234** 0.7789 0.9798

Publikationen:

[1] Kocher, D. C., Apostoaei, A. I., Henshaw, R. W., Hoffman, F. O., Schubauer-Berigan, M. K., Stancescu, D. O., Thomas, B. A., Trabalka, J. R., Gilbert, E. S., & Land, C. E. (2008). Interactive RadioEpidemiological Program (IREP): a web-based tool for estimating probability of causation/assigned share of radiogenic cancers. *Health Physics* , *95*(1), 119–147. https://doi.org/10.1097/01.HP.0000291191.49583.f7