# Does Deep Inspiration Breath-Hold prolong life? Individual Risk Estimates of Ischemic Heart Disease after Breast Cancer Radiotherapy

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## Summary

The radiation exposure of the heart during left-sided breast cancer irradiation increases the risk of ischemic heart disease. Deep inspiration breath-hold techniques can significantly reduce this exposure but are not yet widely used. In a comparative modelling study, we estimated expected individual benefits from deep inspiration breath-hold. Our results suggest that patients with high cardiovascular baseline risk and favourable tumour prognosis benefit most, and that age at treatment has only minor impact.

## Abstract

*Purpose*

Aim of the current comparative modelling study was to estimate the individual radiation-induced risk for death of ischemic heart disease (IHD) under free breathing (FB) and deep inspiration breath-hold (DIBH) in a real-world population.

*Materials and Methods*

Eighty-nine patients with left-sided early breast cancer were enrolled in the prospective SAVE-HEART study. For each patient three-dimensional conformal treatment plans were created in FB and DIBH and corresponding radiation-induced risks of IHD mortality were estimated based on expected survival, individual IHD risk factors and the relative radiation-induced risk.

*Results*

For treatments in FB, the mean calculated absolute 10-year IHD mortality risk was 0.14% and the lifetime risk was 1.6%. With the use of DIBH, mean heart doses and, correspondingly, estimated IHD risks were reduced by 35% (interquartile range: 23% - 46%) as compared to FB. Mean expected years of life lost (YLL) due to radiation-induced IHD mortality were 0.11 years in FB, and 0.07 years in DIBH. YLL were remarkably independent of age at treatment in patients with a favourable tumour prognosis. DIBH led to more pronounced reductions in YLL in patients with high baseline risk (0.08 years for upper vs. 0.02 years for lower quartile), with favourable tumour prognosis (0.05 years for patients without vs. 0.02 years for those with lymph-node involvement), and in patients with high mean heart doses in FB (0.09 years for doses >3 Gy vs. 0.02 years for doses <1.5 Gy).

*Conclusions*

In view of the large number of breast cancer survivors, heart radiation exposure is an important risk factor for IHD. The DIBH technique is an effective countermeasure and should best be offered to all patients with left-sided breast cancer. However, highest benefits are expected for patients with a favourable tumour prognosis, high mean heart dose or high baseline IHD risk, independent of their age.

## Introduction

In the light of continuously improving long-term breast cancer (BC) survival rates [1], minimizing therapeutic morbidity has become a major topic of concern. The risk of heart disease mortality is significantly higher in women after radiotherapy as known from retrospective long-term follow-up data of randomised trials [2]. The results of a population-based case-control study of 2,168 BC patients showed a linear correlation of the relative risk for major coronary events by 7.4% per Gray (Gy) increase in mean heart dose [3]. Furthermore, an analysis of standard tangential radiotherapy for left-sided breast cancer found that parts of the heart still receive significant radiation doses with three-dimensional conformal radiation techniques [4]. Therefore, decreasing the heart dose in BC patients is of fundamental importance.

As a result, advanced radiotherapy techniques, such as respiratory-gated radiotherapy using deep inspiration breath-hold (DIBH), have lately been introduced into clinical practice [5]. During DIBH the distance between the heart and the irradiated target volume (chest wall/breast) increases – which results in a significant reduction of cardiac dose exposure [6]. Even though, in some countries, DIBH is already routinely applied, it cannot be extensively used in most other countries. Thus, there is an important gap in the current evidence base. If the DIBH technique cannot be offered to all patients: which patients benefit most from DIBH?

Due to the slow progression of ischemic heart disease, so far, no randomized studies have been able to quantify the clinical long-term benefit of the DIBH technique. Therefore, aim of the present comparative modelling study was to estimate individual risks of ischemic heart disease (IHD) after BC radiotherapy in a real-world population. Individual cardiovascular risk factors, tumour stage, and age at treatment were used to estimate the impact of DIBH on lifetime risks for coronary heart disease mortality.

## Materials and methods

*Patients*

The prospective SAVE-HEART study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committee of the LMU medical faculty (13.09.2016, No. 355-16) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00011213). Inclusion criteria were informed consent, left-sided breast cancer or carcinoma in-situ and patient compliance for DIBH (ability of breath-hold for 20 seconds).

*Treatment planning*

Every patient received two planning CT scans and treatment plans, one in free breathing (FB) and one in DIBH. The DIBH during CT simulation and treatment delivery was performed using the surface-based Catalyst™/Sentinel™ system as described elsewhere [6] and treatment planning was performed using the Oncentra 4.5.2 software (Elekta, AB, Stockholm). The clinical target volume (CTV) was delineated according to the RTOG contouring atlas [7] and ESTRO consensus guideline [1], the heart according to the CT-based atlas by Feng et al. [8].

*Risk estimates*

Estimates on individual risks of heart disease were based on the SCORE prediction formula [9], evaluated for coronary heart disease mortality for countries with comparatively low cardiac risk. Besides age ($a$), SCORE takes into account the following individual risk factors ($\boldsymbol{r}$): cholesterol level, systolic blood pressure and smoking. From this information, the individual sporadic relative risk as compared to the general population was calculated as:

$$RR^{IHD}(e,\boldsymbol{r}) = \frac{h^{IHD}_{SCORE}(e,\boldsymbol{r})}{h^{IHD}_{pop}(e)}$$

Here, $h^{IHD}_{SCORE}(e,\boldsymbol{r})$ denotes the individual annual risk (hazard) rate and corresponds to the negative derivative of the logarithm of the survival function as given in eq. (3) of ref. [9]. The sporadic relative risk $RR^{IHD}$ was evaluated at the age of treatment ($e$) and was assumed to be independent of age. By this assumption, the typical age-dependent increase in risk due to worsening of risk factors is automatically taken into account. The general population hazard $h^{IHD}_{pop}$ was taken from ref. [10] and interpolated within 5-year strata. It should be noted that $h^{IHD}_{SCORE}$ and $h^{IHD}_{pop}$ are derived from similar populations but there may be some residual deviation in their age dependency. For the radiation-induced risk, the results of Darby et al. [3] were applied, i.e. an excess relative risk of 7.4% per Gray mean heart dose $d$. Taken together, individual hazard rates were estimated:

$$h^{IHD}(a,e,d,\boldsymbol{r}) = h^{IHD}_{pop}(a)RR^{IHD}(e,\boldsymbol{r})(1 + d \cdot 0.074\ \text{Gy}^{-1})$$

In order to calculate absolute risks, information on total survival is necessary. To estimate the total survival in BC patients, the survival of the general population $S_{pop}$ [11] was adjusted with the relative survival $RS$ of BC patients according to their TNM status [12]:

$$S(a,e,TNM) = \frac{S_{pop}(a)}{S_{pop}(e)}\, RS(TNM, a-e)$$

As data on relative survival were available only up to 15 years after radiotherapy, we extrapolated the relative survival thereafter, based on the relative reduction in relative survival within the five preceding years. Subsequently, to account for the individual contribution of IHD to the expected survival, the individual IHD risk estimates were applied:

$$S(a,e,TNM,d,\boldsymbol{r}) = S(a,e,TNM)\exp\left[\int_e^a -h^{IHD}(t,e,d,\boldsymbol{r}) + h^{IHD}_{pop}(t)\cdot(1 + d_m \cdot 0.074\ \text{Gy}^{-1})\,dt\right]$$

The relative survival in BC patients results from many causes of death, some of which may be radiation-induced. Therefore, to compensate for the individually estimated contribution of IHD mortality $h^{IHD}(t,e,d,\boldsymbol{r})$, the average IHD mortality risk was added. It was approximated by the hazard in the general population times a radiation dependent factor. We used $d_m = 2.5$ Gy, the average mean heart dose in the study cohort under FB. However, results are quite insensitive to this value: for example, mean years of life lost (see below) due to irradiation under FB would change by a factor of 1.03 if $d_m = 5$ Gy was assumed.

Using these functions, absolute IHD mortality risks were calculated:

$$AR(a,e,TNM,d,\boldsymbol{r}) = \int_e^a h^{IHD}(t,e,d,\boldsymbol{r})\, S(t,e,TNM,d,\boldsymbol{r})dt$$

For $a = e + 10$ years, this corresponds to the often-encountered 10-year-risks; for $a = 80$ years, it corresponds to the cumulative risk until the age of 80. For lifetime risks $a = 100$ years was assumed. To calculate the excess risks due to radiation, the difference to $AR(a, e, TNM, d = 0, \boldsymbol{r})$ was evaluated. Finally, years of life lost due to the detrimental effects of irradiation on IHD were calculated as:

$$YLL(e, TNM, d, \boldsymbol{r}) = \int_{e}^{100} S(t, e, TNM, 0, \boldsymbol{r}) - S(t, e, TNM, d, \boldsymbol{r}) dt$$

All analyses were performed with MATLAB, version R2017b. Integrals were approximated by sums.

## Results

*Patient characteristics*

One hundred and seven consecutive patients with left-sided breast cancer were enrolled in the prospective SAVE-HEART study since November 2016, and were assessed for cardiovascular risk factors including cholesterol levels, blood pressure and smoking habits. For 18 patients, the SCORE prediction formula was not applicable (8 patients with diabetes, 8 younger than age 40, and 4 older than age 75) and they were excluded from the present analysis. Descriptive statistics on risk factors and tumour characteristics in the remaining 89 patients are presented in table 1. Application of the SCORE risk prediction formula revealed that the estimated IHD mortality risks were close to the general population rates on average but showed large individual variability (median of sporadic relative risk $RR^{IHD}$: 1.0, range: 0.27-3.9). Moreover, there was a trend in the estimated relative risks with increasing age (mean $RR^{IHD}$ for patients below/above the age of 60 years was 1.0/1.5).

| | |
|---|---|
| Treatment age [years] | Mean 57, range 42-73, median 57, IQR 51-62 |
| Total cholesterol [mg/dl] | Mean 223, range 137-321, median 222, IQR 198-247 |
| Systolic blood pressure [mmHg] | Mean 130, range 96-188, median 125, IQR 116-140 |
| Smoking | |
| Yes | 13 (15%) |
| No | 76 (85%) |
| Tumour size | |
| Tis | 12 (13%) |
| T1 | 49 (55%) |
| T2 | 23 (26%) |
| T3 | 4 (4%) |
| T4 | 1 (1%) |
| Nodal status | |
| N0 | 65 (73%) |
| N+ | 18 (20%) |
| Nx | 6 (7%) |

Table 1: Risk factors and tumour characteristics of 89 breast cancer patients between ages 40 and 75. IQR: Interquartile range.

*Mean heart doses*

Mean heart doses in FB were in the range of 0.9 Gy to 9.1 Gy with an average of 2.5 Gy. In DIBH, they ranged from 0.6 Gy to 5.1 Gy with an average reduction of 0.9 Gy. Relative to doses in FB, mean heart doses in DIBH decreased by 35% (interquartile range: 23% to 46%). Only in one single patient, DIBH led to an increased planned mean heart dose, with a minimal difference of 0.04 Gy. The frequencies of occurrence of mean heart doses in FB and DIBH, as well as the individual reductions are presented in figure 1.

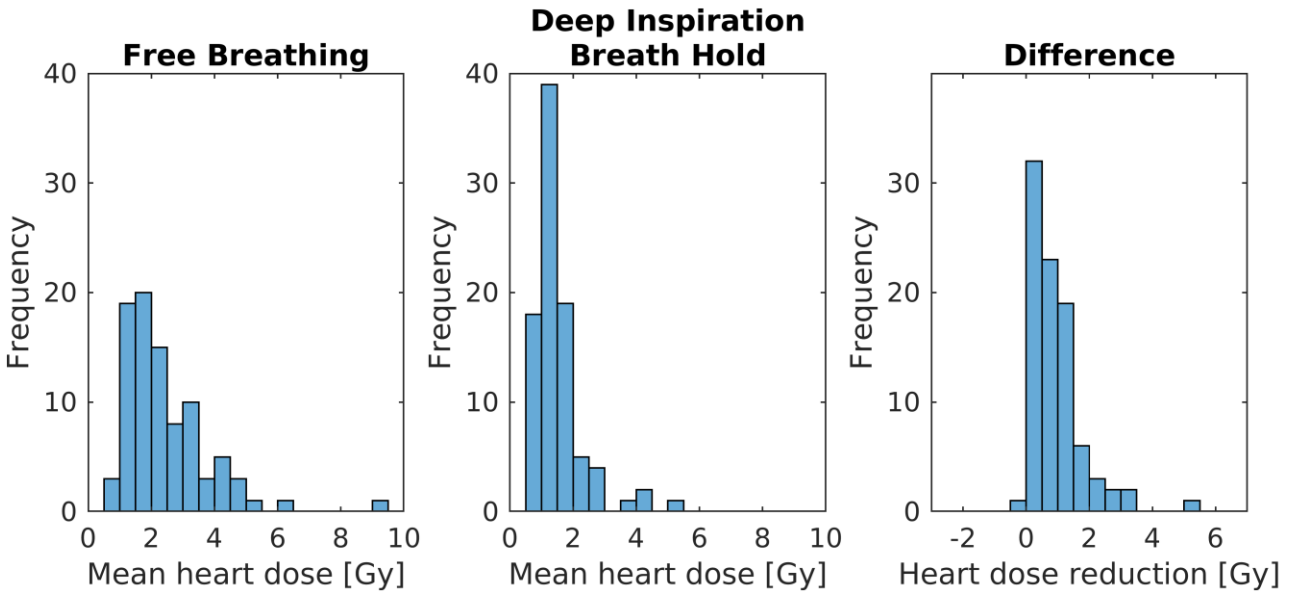


Fig 1: Histograms of mean heart doses in free breathing and deep inspiration breath-hold for 89 patients with left-sided breast cancer radiotherapy. The third panel shows the frequency of mean heart dose reductions in deep inspiration breath-hold as compared to free breathing.

*Risk estimates in free breathing*

For the entire patient cohort, a mean 10-year absolute radiation-induced IHD mortality risk of 0.14% was estimated for treatments in FB. For 16 patients who were 65 years or older, the mean 10-year absolute risk was estimated to 0.47%. This constitutes a seven-fold risk compared to patients below an age of 65. Figure 2 shows how the absolute radiation-induced IHD mortality risk accumulates with age in two exemplary patients of the cohort. As IHD mortality is overall very rare in young and middle-aged women, the first 10 years after radiotherapy contribute very little to the lifetime risk of both patients. One of the patients (no. 17) has an early-staged breast cancer with good prognosis and is thus more likely to reach high ages. For higher ages, radiation-induced IHD mortality is more frequent, and adds to a lifetime risk of about 1.4%. For the second exemplary patient (no. 60) with poor tumour prognosis, the estimated total survival until an age of 80 years is only about 5%. Therefore, radiation-induced IHD death is less likely to occur.
The mean radiation-induced lifetime risk for the entire cohort was estimated to 1.6% in FB, and the cumulative risk until the age of 80 years was 0.4%.

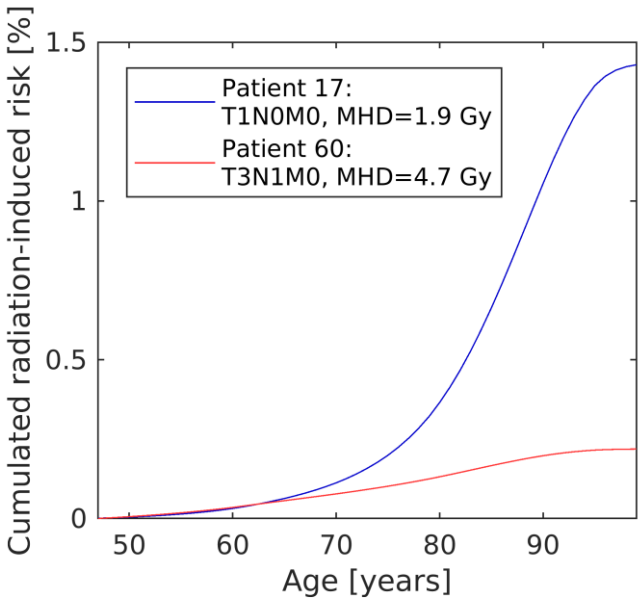


Fig 2: Individual estimated radiation-induced IHD mortality risk cumulative from treatment up to a given age, exemplary for two young patients of the present cohort. Patient no. 17 has a good prognosis and relatively low mean heart dose while patient no. 60 has a more advanced stage of breast cancer and a higher mean heart dose.
MHD: Mean heart dose in free breathing.

*Estimated years of life lost comparing free breathing and deep inspiration breath-hold*

As radiation-induced IHD mortality can occur late in life, estimated years of life lost (YLL) may offer a more intuitive understanding of risks. The mean of YLL due to radiation induced IHD mortality was calculated as 0.11 years in FB, and 0.07 years in DIBH. The reduction in YLL with DIBH as compared to FB was higher in patients with good prognosis (0.05 years for patients without vs. 0.02 years in those with lymph node involvement), in patients with high mean heart doses in FB (0.09 years for doses above 3 Gy vs. 0.02 years for doses below 1.5 Gy) and in patients with high sporadic cardiovascular relative risk (0.08 years for upper quartile vs. 0.02 years for lower quartile). Age at diagnosis was a less important predictor and – in contrast to first intuition – reduction in YLL was higher in older patients (0.05 years for patients above an age of 60 vs. 0.04 years for patients below an age of 60). The distribution of the YLL for the cohort is shown in figure 3.

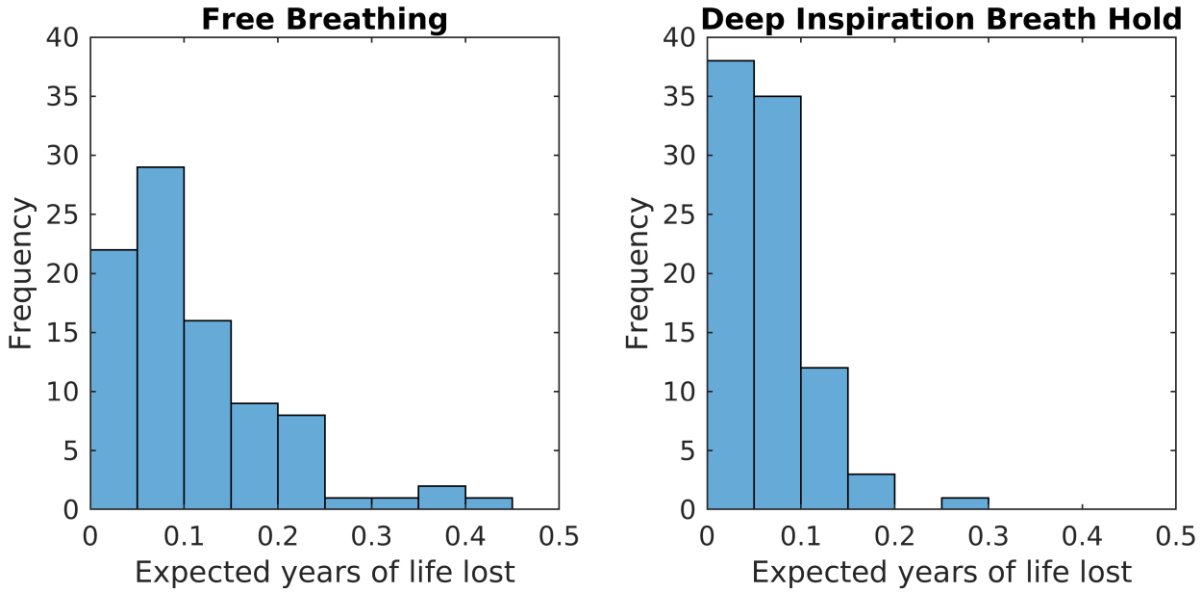

Fig 3: Histograms of individually estimated years of life lost due to radiation-induced IHD mortality in free breathing or deep inspiration breath-hold for 89 patients with left-sided breast cancer.

## Discussion

In the present study, the heart received an average mean dose of 2.5 Gy when the patients were allowed to breathe freely during the treatment. In contrast, a recent review of heart doses in modern radiotherapy [13] showed typical mean heart doses in the treatment of left-sided BC, which even exceeded 5 Gy. In order to reduce the dose to the heart, respiratory gating using a breath-hold procedure has been introduced into the clinical routine. There are different strategies for implementing the DIBH technique in terms of used equipment, required accessories, intra-fractional monitoring and patient feedback systems. Several studies have confirmed the substantial impact of DIBH on dosimetric endpoints, such as mean heart or ipsilateral lung dose [6 14-16]. The dosimetric findings of the present study with a relative reduction of 35% (interquartile range: 23% to 46%) mean heart dose by DIBH are in line with this literature. Since the present study has already achieved comparatively low heart doses in FB, it can be assumed that the absolute benefits of DIBH in other centres or patient groups could be correspondingly higher than in this study.

As recently mentioned in a systematic review of Sardaro et al. [17], only few studies have analysed the role of cardiac baseline risk factors on lifetime risks for coronary heart disease mortality [18]. To the best of our knowledge, this is the first study addressing this issue for a “real-world” patient population. The present comparative modelling study analysed the impact of DIBH on lifetime risks for coronary heart disease mortality by taking the role of individual cardiovascular risk factors, tumour stage, and age at treatment into account. Moreover, it quantifies the expected benefit of DIBH. Finally, radiation induced risk will be contrasted with risks of common risk factors below.

*Risk dependence on treatment age and other individual risk factors*

Age at treatment is often considered a key factor regarding late health risks, and physicians may intuitively prefer young patients for selection of advanced treatment techniques. In contrast to this common expectation, only minor differences in estimated years of life lost were seen comparing patients in the cohort above and below an age of 60 years. To analyse the age dependence independently of individual risk factors, we have calculated the expected years of life lost for two

fictitious patients. For both patients, sporadic risks are assumed to follow national mortality rates and radiation risks are estimated from a mean heart dose of 2 Gy. However, the two patients differ in their assumed prognosis, corresponding to tumour stages T1N0M0 and T3N+M0, respectively.

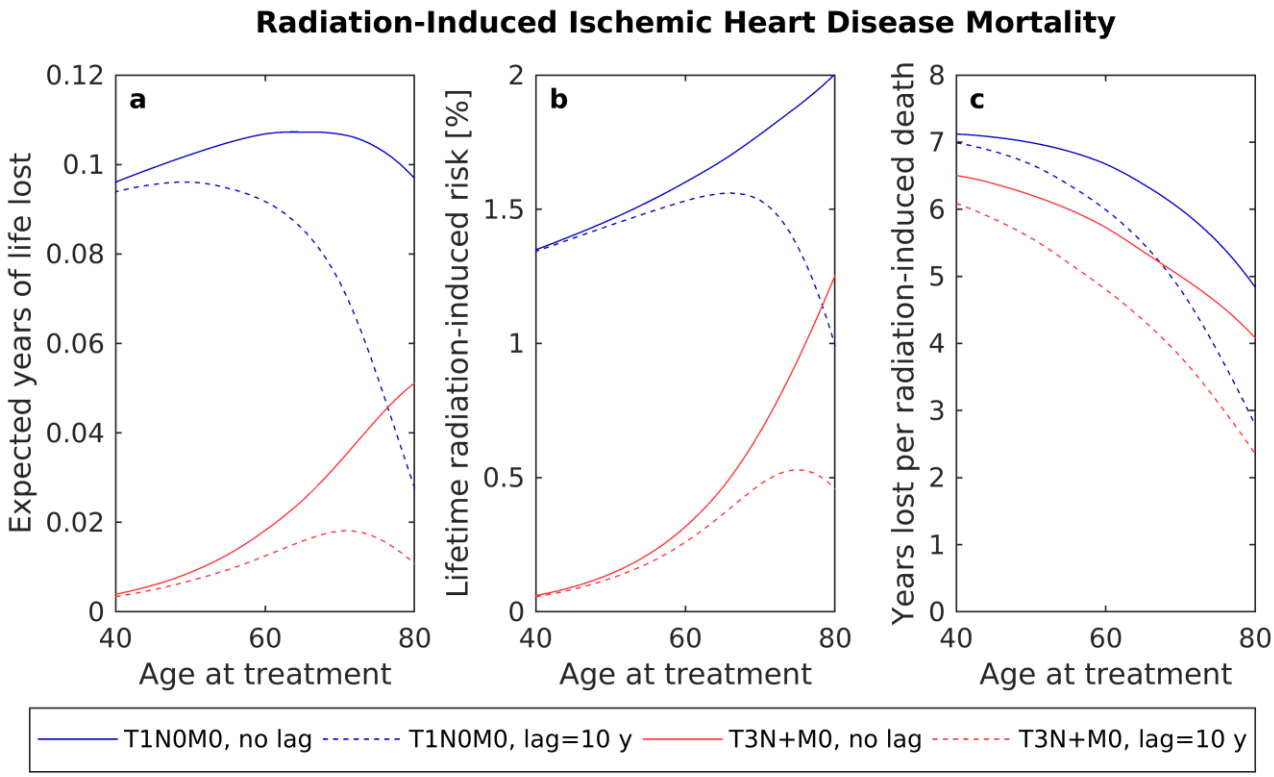


Fig 4: Different risk metrics of radiation-induced IHD mortality as dependent on treatment age for two fictitious patients with normal risk factors and 2 Gy mean heart dose. Immediate radiation effect was presumed for the solid lines while for the dashed lines it was assumed that radiation risk sets in 10 years after treatment. The right panel shows the average expected years of life lost per radiation-induced death. It is obtained from the ratio of expected years of life lost to the lifetime radiation-induced risk.

For the patient with an early-stage T1N0M0 breast cancer, the expected years of life lost are remarkably independent of age at treatment (see figure 4a). With increasing treatment age, the years of life lost associated with a radiation-induced IHD death decrease (figure 4c). However, this is largely compensated by an increase in the absolute risk for IHD mortality (figure 4b). This increase in absolute radiation-induced risk can be attributed to the fact that the older the patient already is, the more likely she will reach an age where IHD death is frequent. Consequently, for patients with poor prognosis and limited expected survival, this increase in the lifetime IHD risk is even more pronounced.

An important issue for the age dependence is a possible lag-time. So far, there is conflicting evidence on whether radiation-induced coronary risk sets in shortly after treatment [3] or increases with a lag-time following exposure [19]. If radiation-induced processes took e.g. 10 years before they manifest in a raised IHD risk, expected years of life lost would be substantially reduced for patients treated above ages of about 70 years, see figure 4a.

To summarize, treatment age is a rather weak predictor of the expected risk. For patients with poor tumour prognosis IHD risks are overall very low but increase with treatment age.

In addition to tumour prognosis, other predictors were strongly associated to YLL. There was large variation in sporadic and radiation risks by cardiovascular risk factors albeit patients were selected without major cardiovascular preconditions and without diabetes. For example, for two 50-year-old

patients (smoker, 157 mmHg systolic blood pressure, 246 mg/dl cholesterol and non-smoker, 104 mmHg, 165 mg/dl) risks differ by a factor of 9.
Mean heart dose may be regarded as another individual factor as it depends on the individual anatomy. The relative dose reduction by DIBH was almost independent of the mean heart dose in FB. As a result, DIBH led to higher absolute reductions in doses and risks in patients with higher mean heart dose in FB.

*Comparison of radiation therapy with the detriment of other risk factors*

To estimate years of life lost due to other risk factors, we also derived the expected lifetime for altered risk factors: First, if the 13 smokers in the patient group were non-smokers, their estimated life expectancy would be larger by 0.5 years on average. Second, if the 22 patients with systolic blood pressure above 140 mmHg had a pressure of 140 mmHg, their life expectancy would be larger by 0.3 years. Third, if the 27 patients with cholesterol level above 240 mg/dl had a cholesterol level of 240 mg/dl, their life expectancy would be larger by 0.1 year. Of course, these numbers take only into account mortality due to IHD. Compared to these estimates, radiation exposure is the most important risk factor regarding IHD mortality when referring to the entire study cohort.

*Limitations*

The radiation risk estimates are based on a number of assumptions, including applicability of the underlying general population and BC patient data, extrapolation of the relative survival of BC patients beyond 15 years, linearity of the dose-response relationship and use of mean heart dose, ignoring the potential impact of higher exposure to some substructures of the heart. Moreover, estimates were based on the relative risk assumption, meaning that radiation risks add multiplicatively to individual IHD risks. The relative risk assumption is commonly used in epidemiological studies and was tested in ref. [3]. The extent to which the relative risk assumption may apply to patients with major cardiovascular preconditions is uncertain. Therefore, those were excluded from the study.
This manuscript deals with IHD mortality only, for which there is good evidence of radiation effects down to doses typically encountered in BC therapy and even below [3 20 21]. Other radiation-induced heart diseases [22 23] may add to the risk. Furthermore, it is expected that DIBH can reduce the exposure of other organs outside the main radiation fields, which contribute to the risk of radiation-induced secondary cancer.

## Conclusions

The absolute risk of radiation-induced IHD mortality due to breast cancer radiotherapy may be regarded as modest when compared to other risks associated with cancer therapy. Nevertheless, the heart exposure is a major IHD risk factor in patients with left-sided breast cancer. The deep inspiration breath-hold technique can effectively reduce this exposure. The corresponding effect on life expectancy appears to be determined rather by individual prognosis and cardiovascular risk factors as compared to age at treatment.

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