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Cardiac late effects after 3D-conformal radiotherapy in female breast cancer patients in Germany

Kardiale Spätfolgen nach 3D-konformaler Strahlentherapie bei Brustkrebspatientinnen in Deutschland

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Abstract

Objective

Radiotherapy is routinely considered as a risk factor for cardiac late effects in female breast cancer patients in epidemiological studies with treatment until the 1990s. However, in the late 1990s radiotherapy made a shift from conventional 2D radiotherapy to 3D-conformal radiotherapy based on computed tomography scans. While this resulted in a reduction of radiation exposure to the heart during radiotherapy, the heart remains exposed. Epidemiological studies with long-term follow-up and information on modern radiotherapy after 2000 are sparse. The overall objective of this thesis is to evaluate the potential risk for cardiac late effects of 3D-conformal radiotherapy, especially after 2000, in female breast cancer patients in Germany based on a multicenter epidemiological study.

Background

Female breast cancer is a major global health burden. It is the most commonly diagnosed cancer worldwide. In many countries the 5-year relative survival exceeds 80%. The high survival rate combined with the demographic transition towards an older population lead to an expanding population at risk for potential adverse late effects of cancer therapy. A cornerstone in breast cancer therapy, radiotherapy reduces local recurrence and breast cancer-related mortality. Despite these benefits, radiotherapy may expose the heart to ionizing radiation, potentially leading to macro- and microvascular damage that can take decades to become clinically relevant. A number of epidemiological studies on the risk for cardiac late effects in female breast cancer patients have been published for the treatment era before 2000, including mainly older radiotherapy regimes with conventional 2D treatment planning. Studies on the risk for cardiac late effects in female breast cancer patients with contemporary 3D-conformal radiotherapy are still sparse, especially for Germany. This cumulative PhD-thesis addresses this gap on the basis of epidemiological analyses of the ESCaRa-Study (Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients).

Research questions

This cumulative PhD-thesis is based on two internationally published epidemiological articles that investigate important questions on cardiac late effects in female breast cancer patients after 3D-conformal radiotherapy. In particular, the articles provide insight regarding the risk for cardiac late effects in the

German setting for contemporary radiotherapy regimes with long-term follow up and individual dosimetry. No results from studies with similar scope and scale have been previously reported. Thus, the two articles' contribution are especially valuable to inform medical decision making on the application of radiotherapy. The main research questions of this thesis are outlined below:

1) Is the risk for long-term cardiac mortality increased in women with 3D-conformal radiotherapy for left-sided breast cancer compared to women with right-sided breast cancer? (Article I)

2) Is the risk for long-term cardiac morbidity increased in women with 3D-conformal radiotherapy for left-sided breast cancer compared to women with right-sided breast cancer? (Article I)

3) Is the risk for long-term cardiac events associated with mean dose from 3D-conformal radiotherapy for female breast cancer to the complete heart or the left anterior heart wall (LAHW) including the left anterior (LAD) coronary artery descending? (Article II)

4) Is the risk for long-term cardiac events associated with the dose-volume metric V5Gy from 3D-conformal radiotherapy for female breast cancer to the complete heart or the left anterior heart wall (LAHW) including the left anterior (LAD) coronary artery descending? (Article II)

Summary Article I

Tumour laterality is frequently used as a proxy for radiation exposure to the heart in epidemiological studies on radiotherapy in female breast cancer patients to assess the risk for cardiac late effects. Due to the anatomical position of the heart in the mediastinum, left-sided breast cancer patients have higher heart-exposure from radiotherapy compared to patients with right-sided tumours. Tumour laterality is mostly random, which enables an unbiased analysis in a quasi-randomized study design, with unknown confounders distributed equally in both groups.

In Article I of this cumulative PhD-thesis results of the ESCaRa cohort are presented. In this article cardiac mortality and cardiac morbidity after radiotherapy in female breast cancer patients in Germany was assessed. A total of 11,982 female breast cancer patients with cancer treatment between 1998-2008 were included. To answer research question 1) a mortality follow-up until 06/2018 was conducted. In order to answer research question 2) cardiac morbidity occurring after breast cancer treatment was assessed via a questionnaire that was sent out in 2014 and 2019. As a proxy for radiation exposure to the heart and to

investigate the effect on cardiac mortality and morbidity tumour laterality of the breast cancer was used. All irradiated patients received 3D-conformal radiotherapy. Cox proportional hazards regression analysis were carried out, taking potential confounders into account. Missing values were imputed by multiple imputation.

After a median mortality follow-up of 11.1 years, there was no statistically significant association of tumour laterality with cardiac mortality comparing left-sided versus right-sided tumours (hazard ratio (HR) 1.09, 95% confidence interval (CI) 0.85-1.41) among irradiated patients. The same holds for cardiac morbidity (HR 1.05, 95% CI 0.88-1.25) after a median follow-up of 12.4 years. The results of Article I are generally in line with other international studies on long-term cardiac mortality in breast cancer patients with contemporary radiotherapy techniques such as 3D-conformal radiotherapy using tumour laterality as a proxy for cardiac dose. Studies on cardiac morbidity on the other hand show conflicting results. In short, a number of studies did reveal an increased risk for both older and more recent therapy regimes including the years 1989-2005, 1977-1989 and 2001-2005, 1999-2005, and 1976-1989 and 1990 onwards. While other studies did not show any association of tumour laterality and cardiac morbidity after radiotherapy for breast cancer for the years 1998-2008, 2000-2009, 1996-2010, and 2008-2016. Although radiotherapy for left-sided breast cancer on average results in higher doses to the heart than radiotherapy for right-sided tumours, no evidence was identified that tumour laterality is a strong risk factor for both cardiac mortality and cardiac morbidity in Article I after 3D-conformal radiotherapy. However, it cannot be ruled out that a larger sample size and longer follow-up would have altered the results. Furthermore, tumour laterality is a crude proxy measure for the actual individual radiation dose to the heart. It does not take into account potential sensitive functional substructures of the heart and does not allow to conduct a dose-response analysis.

Summary Article II

To overcome the aforementioned limitations of using tumour laterality as a proxy for cardiac exposure to ionizing radiation in breast cancer radiotherapy, individual retrospective dosimetry of radiation exposure of the heart during 3D-conformal radiotherapy was used in Article II of this thesis to estimate a potential dose-response relationship. Considerable variability in radiation exposure to the heart and functional substructures was reported for radiotherapy in female breast cancer patients due to individual anatomy and varying field geometries. A dose-response analysis using individual dosimetry for the complete heart and functional substructures enables to estimate a potential dose-response relationship for cardiac late

effects. Studies using individual dose estimates to assess the risk for cardiac late effects in female breast cancer patients are sparse and for Germany so far non-existent. With Article II of the cumulative PhD-thesis this research gap for Germany was targeted.

In the ESCaRa cohort of 11,982 female breast cancer patients diagnosed in 1998-2008, 494 women treated with 3D-conformal radiotherapy and a subsequent cardiac event were selected. Within a nested case-control approach, these cases were matched to 988 controls. Controls were patients without a cardiac event after radiotherapy until the index date of the corresponding case. A cardiac event was defined as either death from a cardiac cause such as a cardiac infarction or the diagnosis of a cardiac disease such as congestive heart failure. To answer research questions 3) and 4) separate multivariable conditional logistic regression models were used. For 91 cases and 182 controls of the 494 cases and 988 controls individual estimates for DMEAN (the volume weighted mean dose) and V5Gy (the volume that received ≥5 Gray (Gy)) values for the complete heart and the LAHW were extracted from the dosimetry sample. For the remaining 403 cases and 806 controls that were not part of the dosimetry sample, doses were imputed based on a validated prediction model.

Over 75% of the cases and controls received radiotherapy treatment >2000. The retrospective dosimetry showed a mean dose to the heart of 4.27 Gy (1.21 Gy-11.98 Gy) for left-sided radiation in cases and 4.31 Gy (0.80 Gy-13.56 Gy) for controls and 1.64 Gy (0.44 Gy-6.10 Gy) and 1.66 Gy (0.56 Gy-13.56 Gy) for right-sided radiation, respectively. The dose-response analysis for DMEAN of the complete heart did not reveal any association with cardiac events (odds ratio (OR) per 1 Gy increase 0.99, 95% CI 0.94-1.05, p=.72) nor a linear dose-response relationship. Likewise, the analysis of DMEAN for the LAHW did not reveal any dose-response relationship for cardiac events (OR per 1 Gy increase 1.00, 95% CI 0.98-1.01, p=.68). Analyses for V5Gy for the complete heart (OR per 1% increase 1.00, 95% CI 0.99-1.01, p=.98) as well as for the LAHW (OR per 1% increase 1.02, 95% 0.79-1.32, p=.88) did not reveal any dose-response relationship either. Results were consistent across all analyses when comparing risk estimates and corresponding CI for adjusted and unadjusted models. Previous dose-response analyses including mostly patients treated up to the year 2000 provided evidence that radiation dose to the heart from radiotherapy is linearly associated with an increasing risk for cardiac morbidity and cardiac mortality. Contrary to previous studies, the analysis of Article II provides no evidence that radiation dose to the heart from 3D-conformal radiotherapy for female breast cancer patients treated mainly after 2000 was associated with cardiac late effects. Besides the different treatment period, comparability to previous studies is hampered by heterogeneity in aspects of study design including the definition of the endpoint, inclusion criteria, matching criteria and the use of latency time.

Conclusion

In summary, the results of this cumulative PhD-thesis reassure the relatively safety of modern radiotherapy techniques such as 3D-conformal radiotherapy. The findings suggest that 3D-conformal radiotherapy for female breast cancer is not associated with a significantly increased risk for cardiac late effects. This might be interpreted as a result of the extensive efforts to spare the heart as an important organ at risk during radiotherapy, taking into account patient co-morbidities as well as chemotherapy, and providing follow-up care. However, as the results differ from previous international dose-response analyses further independent studies with a comparatively recent treatment period and long follow-up are needed to verify the findings.

Outlook

The following options could be considered as an outlook for future research. First, in an explorative analysis other substructures of the heart and other dose metrics could be investigated as for the complete heart and the LAHW both DMEAN and V5Gy were not associated with an increased risk for cardiac late effects. Further substructures to consider would be e.g. the aortic valve or the pulmonary valve. Additional alternative dose metrics to consider could be the relative volume exposed to at least 10 Gy (V10Gy) or the dose received by the maximally exposed 2 cm^3 (D2CC). Second, based on the available computed tomography scans a coronary artery calcium score could be retrospectively determined in ESCaRa. Long before the onset of clinically significant cardiac late effects, subclinical cardiac changes might occur. Identifying patients with high risk for radiation-induced cardiac complications through effective subclinical markers would be beneficial for primary and secondary prevention. A score could be used to identify these patients with a higher risk for coronary artery diseases and would therefore provide additional new evidence on cardiac effects in breast cancer patients after 3D-conformal radiotherapy from this cohort. Third, to increase the number of events and enable to estimate more robust effect estimates, additional years of follow-up by a continuation of the systematic individual mortality follow-up via the corresponding compulsory population registries of the municipalities and an additional questionnaire on cardiac morbidity could be added. Alternatively, and potentially even more useful, a pooled analysis based on original data of the previous studies including data of the ESCaRa dose-response study with individual retrospective dosimetry on cardiac late effects after radiotherapy in female breast cancer patients could be conducted.

Zusammenfassung

Ziel

Die Strahlentherapie bei weiblichen Brustkrebspatientinnen gilt als Risikofaktor für kardiale Spätfolgen. Ein Großteil der Evidenz stammt aus epidemiologischen Studien die Strahlentherapieregime vor dem Jahr 2000 einschließen. In den späten 1990er-Jahren vollzog sich ein Wechsel in der Strahlentherapie von der konventionellen 2D Strahlentherapie hin zur 3D-konformalen Strahlentherapie auf Basis von computertomographischer Bildgebung. 3D-konformale Strahlentherapie führte zu einer Verringerung der Strahlenbelastung des Herzens während der Strahlentherapie. Nichtsdestotrotz bleibt das Herz exponiert und epidemiologische Studien zu 3D-konformalen Strahlentherapie und kardialen Spätfolgen bei Patientinnen mit einer Therapie nach 2000 mit Langzeit-Follow-up sind spärlich. Ziel dieser kumulativen Dissertation ist die Bewertung des potenziellen Risikos für kardiale Spätfolgen nach 3D-konformaler Strahlentherapie, insbesondere nach 2000, bei weiblichen Brustkrebspatientinnen auf Grundlage einer multizentrischen epidemiologischen Studie.

Hintergrund

Brustkrebs bei Frauen ist eine globale Herausforderung. Weltweit ist Brustkrebs bei Frauen die am häufigsten diagnostizierte Krebserkrankung. In vielen Ländern liegt die relative 5-Jahres-Überlebensrate bei über 80%. Die hohe Überlebensrate in Kombination mit dem demografischen Wandel hin zu einer älteren Bevölkerung, führt zu einer wachsenden Gruppe von Brustkrebspatientinnen, die einem Risiko für potentielle Spätfolgen der Krebstherapie ausgesetzt sind. Die Strahlentherapie ist ein Eckpfeiler der Brustkrebstherapie. Sie verringert das Auftreten von lokalen Rezidiven und der brustkrebsbedingten Sterblichkeit. Ungeachtet dieser Vorteile wird während der Strahlentherapie der Brust das Herz ionisierender Strahlung ausgesetzt. Dies kann zu makro- und mikrovaskulären Schäden führen, welche erst nach Jahrzehnten klinisch relevant werden können. Eine Reihe von epidemiologischen Studien zum Risiko für kardiale Spätfolgen bei Brustkrebspatientinnen wurde für die Behandlungsära vor dem Jahr 2000 veröffentlicht. In diesen Arbeiten wurden hauptsächlich ältere Strahlentherapiesysteme mit konventioneller 2D Behandlungsplanung verwendet. Studien zum Risiko für kardiale Spätfolgen bei Brustkrebspatientinnen nach moderner 3D-konformaler Strahlentherapie sind insbesondere für Deutschland rar. Diese kumulative Dissertation schließt diese Lücke auf der Basis von epidemiologischen Analysen der ESCaRa-Studie (Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients).

Forschungsfragen

Diese kumulative Dissertation setzt sich aus zwei international peer-review publizierten epidemiologischen Fachartikeln zusammen, welche wichtige Fragen zu kardialen Spätfolgen bei Brustkrebspatientinnen nach 3D-konformaler Strahlentherapie behandeln. Die Artikel liefern insbesondere Erkenntnisse über das Risiko kardialer Spätfolgen bei moderner Strahlentherapie in Deutschland, basierend auf einer langen Nachbeobachtungszeit und individueller retrospektiver Dosimetrie. Bisher wurden keine Ergebnisse von Studien mit ähnlichem Umfang und Ausmaß berichtet. Die beiden Artikel können damit besonders wertvolle Beiträge für die medizinische Entscheidungsfindung in der Strahlentherapie bei Brustkrebspatientinnen leisten. Die zentralen Forschungsfragen dieser Dissertation sind:

1) Ist das Risiko für kardiale Mortalität als Spätfolge nach 3D-konformaler Strahlentherapie bei Frauen mit linksseitigem Brustkrebs im Vergleich zu Frauen mit rechtsseitigem Brustkrebs erhöht? (Artikel I)

2) Ist das Risiko für kardiale Morbidität als Spätfolge nach 3D-konformaler Strahlentherapie bei Frauen mit linksseitigem Brustkrebs im Vergleich zu Frauen mit rechtsseitigem Brustkrebs erhöht? (Artikel I)

3) Ist das Risiko für kardiale Ereignisse als Spätfolge bei Brustkrebspatientinnen mit der mittleren Dosis der 3D-konformalen Strahlentherapie des Gesamtherz oder der linken vorderen Herzwand einschließlich der linken vorderen absteigenden Koronararterie assoziiert? (Artikel II)

4) Ist das Risiko für kardiale Ereignisse als Spätfolge bei Brustkrebspatientinnen mit der Dosis-Volumen-Metrik V5Gy der 3D-konformalen Strahlentherapie des Gesamtherz oder der linken vorderen Herzwand einschließlich der linken vorderen absteigenden Koronararterie assoziiert? (Artikel II)

Zusammenfassung Artikel I

Tumorlateralität wird in epidemiologischen Studien zu Spätfolgen nach Strahlentherapie bei Brustkrebspatientinnen häufig als Approximation für die tatsächliche Strahlenbelastung des Herzens verwendet. Aufgrund der anatomischen Lage des Herzens im Mediastinum haben Patientinnen mit

linksseitigem Brustkrebs im Vergleich zu Patientinnen mit rechtsseitigem Tumor eine höhere Strahlenbelastung des Herzens durch die Strahlentherapie. Die Tumorlateralität ist meist zufällig, was eine nicht-verzerrte Analyse in einem quasi-randomisiertem Studiendesign ermöglicht, bei dem unbekannte Störfaktoren in beiden Gruppen gleich verteilt sind.

In Artikel I dieser kumulativen Dissertation werden die Ergebnisse aus der ESCaRa-Studie vorgestellt. In diesem Artikel wurde die kardiale Mortalität und kardiale Morbidität nach Strahlentherapie bei Brustkrebspatientinnen in Deutschland untersucht. Insgesamt wurden 11.982 Brustkrebspatientinnen mit einer Krebsbehandlung zwischen 1998-2008 eingeschlossen. Zur Beantwortung der Forschungsfrage 1) wurde ein Mortalitäts-Follow-up bis 06/2018 durchgeführt. Zur Untersuchung der Forschungsfrage 2) wurde die kardiale Morbidität nach einer Burstkrebsbehandlung mittels eines Fragebogens erhoben, welcher 2014 und 2019 verschickt wurde. Als Approximation für die Strahlenbelastung des Herzens und zur Untersuchung der Auswirkung auf kardiale Mortalität und Morbidität wurde die Tumorlateralität der Brustkrebserkrankung verwendet. Alle bestrahlten Patientinnen erhielten eine 3D-konformale Strahlentherapie. Es wurden Cox-Proportional-Hazard-Regressionsanalysen durchgeführt, wobei für potentielle Störfaktoren adjustiert wurde. Fehlende Werte wurden mittels multipler Imputation bestimmt. Nach einem medianen Mortalitäts-Follow-Up von 11,1 Jahren wurde kein statistisch signifikanter Zusammenhang zwischen der Tumorlateralität und der kardialen Mortalität, beim Vergleich von linksseitigen vs. rechtsseitigen Tumoren beobachtet (Hazard Ratio (HR) 1,09; 95% Konfidenzintervall (KI) 0,85-1,41). Dasselbe gilt für kardiale Morbidität (HR 1,05; 95% KI 0,88-1,25) nach einem medianen Follow-up von 12,4 Jahren. Die Ergebnisse von Artikel I stehen im Einklang mit anderen internationalen Studien zu kardialer Mortalität als Spätfolge bei Brustkrebspatientinnen, die mit 3D-konformaler Strahlentherapie behandelt wurden und ebenfalls Tumorlateralität als Approximation für die kardiale Dosis der Strahlung während der Strahlentherapie verwendet haben. Studien zur kardialen Morbidität als Spätfolge wiederum zeigen widersprüchliche Ergebnisse. Zusammengefasst zeigte sich in einer Reihe von Studien ein erhöhtes Risiko sowohl für ältere als auch neue Therapieregime. Die Studien schlossen die Jahre 1989-2005, 1977-1989 und 2001-2005, 1999-2005 sowie 1976-1989 und >1990. Andere Studien hingegen zeigten für die Jahre 1998-2008, 2000-2009, 1996-2010 und 2008-2016 keinen Zusammenhang zwischen Tumorlateralität und kardialer Morbidität nach Strahlentherapie bei Brustkrebs. Auch wenn die Strahlentherapie bei linksseitigem Brustkrebs mit durchschnittlich höheren Dosen für das Herz einhergeht als bei rechtsseitigen Tumoren, wurden in Artikel I keine Hinweise darauf gefunden, dass die Tumorlateralität ein starker Risikofaktor ist. Dies trifft sowohl auf kardiale Mortalität als auch kardiale Morbidität als Spätfolge nach 3D-konformaler Strahlentherapie zu. Es kann jedoch nicht ausgeschlossen

werden, dass ein größeres Patientenkollektiv und ein längeres Follow-up die Ergebnisse verändert hätten. Ferner ist die Tumorlateralität eine grobe Approximation der tatsächlichen individuellen Strahlendosis des Herzens. Zusätzlich berücksichtigt Tumorlateralität nicht die potenziell empfindlichen funktionalen Substrukturen des Herzens und lässt keine Dosis-Wirkungs-Analyse zu.

Zusammenfassung Artikel II

Um die oben beschriebenen Limitationen bei der Verwendung der Tumorlateralität als Approximation für die kardiale Exposition gegenüber ionisierender Strahlung bei Strahlentherapie von Brustkrebs zu überwinden, wurde in Artikel II dieser Arbeit, basierend auf einer individuellen retrospektiven Dosimetrie der Strahlenexposition des Herzens bei 3D-konformaler Strahlentherapie, eine Dosis-Wirkungs-Analyse durchgeführt. Bei der Strahlentherapie von Brustkrebspatientinnen wurde aufgrund von individueller Anatomie und unterschiedlicher Feldgeometrie eine erhebliche Variabilität der Strahlenexposition für das Herz und funktionale Substrukturen beobachtet. Eine Dosis-Wirkungs-Analyse unter Verwendung von individueller Dosimetrie für das gesamte Herz und funktionelle Substrukturen ermöglicht die Abschätzung einer möglichen Dosis-Wirkungs-Beziehung für kardiale Spätfolgen. Studien, mit individueller Dosimetrie zur Beurteilung des Risikos für kardiale Spätfolgen bei Brustkrebspatientinnen, sind spärlich und für Deutschland bisher nicht vorhanden. Mit Artikel II der kumulativen Dissertation wird diese Forschungslücke für Deutschland adressiert.

Aus der ESCaRa-Kohorte von 11.982 Patientinnen, bei denen zwischen 1998 und 2008 Brustkrebs diagnostiziert wurde, wurden 494 Frauen ausgewählt, die mit 3D-konformaler Strahlentherapie behandelt wurden und bei denen anschließend ein kardiales Ereignis auftrat. Im Rahmen einer eingebetteten Fall-Kontroll-Studie wurden die Fälle 988 passenden Kontrollen zugeordnet. Als Kontrollen wurden Frauen ohne kardiales Ereignis nach Strahlentherapie zum Indexdatum des entsprechenden Falles gezogen. Ein kardiales Ereignis wurde definiert als entweder das Versterben an einer kardialen Ursache wie einem Herzinfarkt oder das Auftreten einer Herzerkrankung wie beispielsweise eine Herzinsuffizienz. Zur Beantwortung der Forschungsfragen 3) und 4) wurden separate multivariable conditional logistische Regressionsmodelle verwendet. Für 91 Fälle und 182 Kontrollen, der insgesamt 494 Fälle und 988 Kontrollen, konnten aus einer separaten Dosimetriestichprobe individuelle Dosisschätzungen für DMEAN (die volumengewichtete mittlere Dosis) und V5Gy (das Volumen, das ≥5 Gray (Gy) erhalten hat) für das gesamte Herz und die linke vordere Herzwand extrahiert werden. Für die verbleibenden 403 Fälle und 806

Kontrollen, die nicht Teil der Dosimetriestichprobe waren, wurden die Dosen auf der Grundlage eines validierten Vorhersagemodells berechnet.

Mehr als 75% der Fälle und Kontrollen erhielten eine Strahlentherapie nach 2000. Die retrospektive Dosimetrie ergab eine mittlere Dosis von 4,27 Gy (1,21 Gy-11,96 Gy) für das Herz bei linksseitiger Bestrahlung bei Fällen und 4,31 Gy (0,80 Gy-13,56 Gy) bei den Kontrollen und entsprechend 1,64 Gy (0,44 Gy-6,10 Gy) und 1,66 Gy (0,56 Gy-13,56 Gy) für rechtsseitige Bestrahlung. Die Dosis-Wirkungs-Analyse für DMEAN des gesamten Herzens zeigte keinen Zusammenhang mit kardialen Ereignissen (Odds Ratio (OR) je 1 Gy 0,99; 95% KI 0,94-1,05; *p*=.72). Auch die Analyse von DMEAN für die linke vordere Herzwand zeigte keinen Dosis-Wirkungs-Zusammenhang für kardiale Ereignisse (OR je 1 Gy 1,00; 95% KI 0,98-1,01; *p*=.68). Die Analysen für V5Gy für das gesamte Herz (OR je 1% 1,00; 95% KI 0,99-1,01; *p*=.98) sowie für die linke vordere Herzwand (OR je 1% 1,02; 95% 0,79-1,32; *p*=.88) zeigten ebenfalls keine Dosis-Wirkungs-Beziehung. Die Ergebnisse waren in allen Analysen konsistent, wenn man die Risikoschätzer und die entsprechenden KI für adjustierte und nicht-adjustierte Modelle vergleicht. Vorangegangene internationale Dosis-Wirkungs-Analysen, die hauptsächlich Patienten mit einer Strahlentherapie vor 2000 eingeschlossen haben, zeigten einen Zusammenhang für die mittlere Strahlendosis des Herzens und kardialen Ereignissen. Der berichtete Dosis-Wirkungs-Zusammenhang in diesen Studien war linear. Im Gegensatz zu früheren Studien liefert die Analyse von Artikel II keine Hinweise darauf, dass die Strahlendosis für das Herz bei der 3D-konformen Strahlentherapie für weibliche Brustkrebspatientinnen, die hauptsächlich nach dem Jahr 2000 behandelt wurden, mit kardialen Spätfolgen assoziiert ist. Die Vergleichbarkeit mit früheren Studien wird durch die Heterogenität im Studiendesign erschwert. Dies umfasst die Definition des Endpunkts, die Einschlusskriterien, die Matchingvariablen und die Verwendung von Latenzzeit.

Schlussfolgerung

Die Analysen dieser Arbeit geben keinen Hinweis darauf, dass die 3D-konformale Strahlentherapie bei weibliche Brustkrebspatientinnen mit einem signifikant erhöhtem Risiko für kardiale Spätfolgen assoziiert ist. Die Ergebnisse dieser kumulativen Dissertation lassen sich als Bestätigung für die relative Sicherheit von moderner Strahlentherapie wie der 3D-konformalen Strahlentherapie bei Brustkrebs interpretieren. Sie lassen sich ebenfalls als Resultat umfangreicher Bemühungen deuten, das Herz als wichtiges Risikoorgan während der Strahlentherapie zu schonen, die Komorbidität sowie die Chemotherapie der Patienten zu berücksichtigen und eine adäquate Nachsorge zu gewährleisten. Da die Ergebnisse der Dosis-Wirkungs-Analyse von früheren Studien dieser Art abweichen, sind weitere unabhängige Untersuchungen

zu vergleichsweise moderner Strahlentherapie mit einer ausreichend langen Nachbeobachtung erforderlich, um die Ergebnisse zu validieren.

Ausblick

Die folgenden drei Optionen können als Ausblick für zukünftige Forschungsvorhaben erwägt werden. Erstens könnten in weiteren explorativen Analysen zusätzliche funktionale Substrukturen wie die Aortenklappe oder die Pulmonalklappe des Herzens sowie weitere Dosismetriken untersucht werden. Als weitere Dosismetriken könnten beispielsweise das Volumen, das mindestens 10 Gy ausgesetzt war (V10Gy) oder die Dosis, die die maximal exponierten 2 cm^3 erhalten haben (D2CC) in Betracht gezogen werden. Zweitens könnten subklinische kardiale Veränderungen untersucht werden. Diese Veränderungen können bereits lange vor dem Auftreten klinisch signifikanter kardialer Spätfolgen präsent sein. Die Identifizierung von Patienten mit einem hohen Risiko für strahleninduzierte kardiale Komplikationen durch zuverlässige subklinische Marker wäre für die Primär- und Sekundärprävention von Vorteil. Auf Grundlage der verfügbaren Computertomographie-Scans könnte in ESCaRa retrospektiv ein Score zur Verkalkung der Koronararterien bestimmt werden. Dieser Score könnte zur Identifizierung von Patientinnen mit einem erhöhten Risiko für koronare Herzkrankheiten verwendet werden. Damit ließen sich zusätzliche Erkenntnisse über die kardialen Auswirkungen bei Brustkrebspatientinnen nach 3D-konformaler Strahlentherapie aus dem vorhandenen Material gewinnen. Drittens könnten robustere Effektschätzer berechnet werden, wenn die Zahl der Ereignisse höher wäre. Dies könnte mittels einem erweiterten Follow-up durch eine Fortsetzung der systematischen individuellen Mortalitätsnachbeobachtung und einem weiteren Fragebogen zur kardialen Morbidität erzielt werden. Alternativ und potentiell noch nützlicher könnte eine gepoolte Analyse auf Basis von Originaldaten sein. Hierzu sollten die früheren Studien mit individueller Dosimetrie zu kardialen Spätfolgen nach Strahlentherapie bei Brustkrebspatientinnen, inklusive der Daten der ESCaRa Dosis-Wirkungs-Studie, eingeschlossen und ausgewertet werden.

List of abbreviations

2D	2-dimensional
3D	3-dimensional
BACCARAT	BreAst Cancer and Cardiotoxicity Induced by Radio Therapy
BRCA	Breast Cancer gene
CAC	Coronary artery calcium
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CT	Computed tomography
DCIS	Ductal carcinoma in situ
DMEAN	Volume weighted mean dose
EBCTCT	The Early Breast Cancer Trialists' Collaborative Group
ER	Estrogen receptor
ESCaRa	Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients
Gy	Gray
HR	Hazard ratio
HER2	Human epidermal growth factor 2
ICD	International Classification of Disease
ICD-10	International Classification of Disease Version 10
ICD-11	International Classification of Disease Version 11
IMRT	Intensity Modulated Radiation Therapy
IRR	Incidence risk ratio
LAD	Left anterior descending
LAHW	Left anterior heart wall
LMIC	Low and middle income countries
MHD	Mean heart dose
MR	Mortality ratio
MRI	Magnetic resonance imaging
mSv	Millisievert
MV	Megavolt
OAR	Organ at risk
OR	Odds ratio
PASSOS	Personalized assessment of late health risks after radiation exposure for optimization of medical application in medicine network
PET	Positron emission tomography
PR	Progesterone receptor
RR	Risk ratio
SEER	Surveillance, Epidemiology, and End Results
sHR	Subdistribution hazard ratio
START	The Standardisation of Breast Radiotherapy
TNM	Tumour-Node-Metastasis
UK	United Kingdom
US	United States
V5Gy	Relative volume exposed to at least 5 Gy
V10Gy	Relative volume exposed to at least 10 Gy
VMAT	Volumetric modulated arc therapy

1 Background

Female breast cancer is a major global health burden. It is the most commonly diagnosed cancer worldwide, with approximately 2.3 million new cases per year [1]. Mammography screening and effective adjuvant therapy resulted in substantial increases in the survival of female breast cancer patients [2 3]. In many countries the 5-year relative survival exceeds 80% [4]. The combination of a high survival rate and the demographic transition towards an older population leads to an expanding population at risk for potential adverse late effects of cancer therapy. This has increased the interest in potential adverse late effects of cancer therapy. A cornerstone in breast cancer therapy, radiotherapy reduces local recurrence and breast cancer-related mortality [5 6]. Despite these benefits, radiotherapy may expose the heart to ionizing radiation, potentially leading to macro- and microvascular damage that can take decades to become clinically relevant [7]. A number of epidemiological studies on the risk for cardiac late effects in female breast cancer patients have been published for the treatment era before 2000, including mainly older radiotherapy regimes with conventional 2-dimensional (2D) treatment planning. Studies on the risk of cardiac late effects in female breast cancer patients with contemporary 3-dimensional (3D)-conformal radiotherapy are still sparse, especially for Germany. This cumulative PhD-thesis issues this gap on the basis of epidemiological analyses of the ESCaRa-Study (Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients).

1.1 Female breast cancer

1.1.1 Breast cancer classification

Breast cancer is defined as a malignant neoplasm of the breast including the connective tissue of the breast, but not the skin of the breast. According to the International Classification of Disease (ICD) Version 10 (ICD-10) breast cancer is coded as C50 [8]. In 2022 ICD Version 11 (ICD-11) was released. In ICD-11 breast cancer is coded as 2C6, which further sub-classifies into 2C60-2C6Z [9].

From a clinical point of view breast cancer cases can be divided into non-invasive and invasive breast cancers [10]. In the case of a non-invasive breast cancer, cells have not extended to tissues outside of the initially affected lobules or ducts. The ductal carcinoma in situ (DCIS) is the most common example for a non-invasive breast cancer. It is limited to the breast duct, and no atypical cells have extended to close proximity of tissues other than the duct [10]. Once abnormal cells extend from within the lobules or ducts into close proximity of the breast tissue, they are called invasive breast cancer [11-13].

Effective treatment planning needs staging of breast cancer. The Tumour-Node-Metastasis (TNM)-based staging system is widely used for breast cancer [14]. The TNM-classification reflects the prognosis of the tumour. For this, it incorporates features of the tumour, the nodes, and potential metastasis. For example, a tumour of a larger size (T3), with more affected lymph nodes (N2), and presence of distant metastasis (M1) generally has a worse prognosis, compared to smaller tumours (T1), with no affected lymph nodes (N0) and absence of distant metastasis (M0). Both, the morphological classification and the TNM-based classification are not completely sufficient to predict the behavior of breast tumour pathophysiology [13]. More recently, with the 2009 St. Gallen Consensus and the updated St. Gallen in 2013, emphasis has been shifted to a molecular classification. Molecular classification further improves clinical management and therapy planning [15] [16]. Studies on gene expression profiles identified four clinically relevant molecular subtypes: Luminal A, Luminal B, HER2+, and Triple Negative [13]. These molecular subtypes are defined by different immunohistochemical biomarkers, namely the three hormone receptors estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) summarized in Table 1 [17]:

Table 1: Classification of molecular subtypes of breast cancer (adapted from [17])

Molecular Subtypes	**Luminal A**	**Luminal B**	**HER2+**	**Triple Negative**
Biomarkers	ER+ PR+ HER2- Ki67low	ER+ PR-/+ HER2-/+ Ki67 high	ER- PR- HER2+ Ki67high	ER- PR- HER2-
Frequency of cases (%)	~40	10-20	10-15	15-20
Prognosis	Best prognosis	Worse prognosis compared to Luminal A	Worse prognosis compared to Luminal cancers	Worst prognosis

ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor 2

1.1.2 Risk factors of female breast cancer

Risk factors for female breast cancer are diverse, including genetic, reproductive, environmental, and lifestyle factors [18]. Regarding genetic factors, women having a first-degree relative with a breast cancer, have an increased risk ratio (RR) of 1.80 (99% confidence interval (CI) 1.69-1.91). Any further first-degree relative with a history of breast cancer further increases the risk for breast cancer [19]. Autosomal dominant mutations in BRCA (BReast Cancer gene) 1 and BRCA 2 might be associated with a 10-fold increased risk for breast cancer [18]. A meta-analysis on BRCA 1 and BRCA 2, including 10 studies containing genotype information and breast cancer risk, showed a mean cumulative cancer risk of 57% (95% CI 47%-66%) for carriers of BRCA 1 at age 70 and 49% (95% CI 40%-57%) for BRCA 2 mutation carriers [20]. Other genetic mutations associated with in increased risk for breast cancer are Li Fraumeni Syndrome and Cowden Syndrome [18].

Presumably, less than 10% of all breast cancer cases can be attributed to an inherited genetic mutation in Western countries [18]. More commonly, breast cancer is associated with a wide range of potential reproductive, environmental and lifestyle factors [18]. For female breast cancer a strong dependence on age is observed. It is rare before the age of 30 years and the risk increases up to 50 years. The risk for breast cancer still increases after 50 years of age, but at a much lower rate [21]. It is hypothesized, that the change in the incidence curve at about 50 years of age is associated with hormonal changes due to menopause [22]. A decrease in circulating estrogen levels and other hormones might affect the progression of malignant mutations in mammary gland cells. This is consistent with observations in epidemiological studies. Late menarche or early menopause showed a protective effect on the risk of female breast cancer due to less menstrual cycles and therefore less exposure to ovarian hormones during the reproductive years [21]. In accordance, early age at first menarche and late age at menopause are associated with an increased risk for breast cancer [23]. Women with a first menarche before the age of 11 have triple the risk of women with later menarche. Having menopause after the age of 55 doubled the risk for breast cancer later in life compared to women with earlier age at menopause [24]. Nulliparity and a late age at first birth are also both associated with an increased risk for breast cancer. Risk for breast cancer for women with the first child after the age of 30 is about twice that of women with a first child at the age of 20. Women with a first child at the age of 35 or older have an even more increased risk, also compared to nulliparous women [24]. Contrary, breastfeeding was associated with a decreased risk for breast cancer. For every 12 months of breastfeeding the relative risk of breast cancer decreased by 4.3% (95% CI 2.9-5.8). Each additional birth also decreased the risk by 7.0% (95% CI 5.0-9.0) [25]. An established environmental risk factor for breast cancer is exposure to ionizing radiation. This has been shown in various settings and study populations [21]

[26]. Based on epidemiological data, a linear dose-response relationship down to low doses of approximately 100 millisievert (mSv) is assumed. Although, the magnitude of risk per unit dose strongly depends on the age of exposure. Generally, younger age at exposure is associated with a higher risk for radiation-associated breast cancer [21]. Beside radiation, a variety of lifestyle factors are discussed in the context of an increased risk for breast cancer [23] [24]. These lifestyle factors include diet [27], weight [28-32], alcohol consumption [33], smoking [33], physical activity [34], oral contraceptives [35], and hormone replacement therapy [36].

1.1.3 Incidence of female breast cancer

Cancer of the breast in women is the most common cancer worldwide. In 2020, female breast cancer has overtaken lung cancer as the most commonly diagnosed cancer, with approximately 2.3 million new cases per year. This accounts for 11.7% of all incident cancer cases [1]. Incidence rates vary worldwide [1] [37]. According to the latest GLOBOCAN estimates, the lowest age-standardized incidence rates, using the 1966 Segi-Doll World standard population, for female breast cancer are observed in South Central Asia (26.2 per 100,000 women) and Middle Africa (32.6 per 100,000 women). The highest age-standardized incidence rates per 100,000 women are observed in North America (86.4), Western Europe (90.7) and Australia/New Zealand (95.5). In general, age-standardized incidence rates for female breast cancer are higher in countries with a high to very high human development index (55.9 per 100,000 women) compared to countries with a low to medium human development index (29.7 per 100,000 women) [1]. In developed countries healthcare infrastructure enables the registration of quality incidence data on cancer with a high completeness. In contrast, in low and middle income countries (LMIC) with a lower human development index, health care facilities are often limited or scarce. This can result in low quality cancer registration data and deficiencies in completeness [38]. Therefore, an underestimation of breast cancer incidence in LMICs is likely. For Germany, the Robert Koch-Institute reports approximately 69,900 newly diagnosed cases of female breast cancer for 2018 [39]. This accounts for an age-standardized rate of 112.6 newly diagnosed cases of female breast cancer per 100,000 women based on the European standard population for age-standardization. The median age of onset in Germany was 64 years [39]. The higher incidence rates for female breast cancer in countries with a high human development index such as Germany is consistent with a higher presence of comprehensive established mammographic screening programs and established risk factors [40]. These risk factors mainly consist of reproductive and hormonal factors such as early age at menarche, late age at menopause, advanced age at first birth, fewer number of children, less breastfeeding, menopausal hormone therapy, and oral contraceptives [1]. Furthermore, a higher prevalence

of lifestyle factors such as alcohol intake, excess body weight, and lack of physical activity might also contribute to the higher incidence rates in countries with a higher human development index [1].

1.1.4 Mortality of female breast cancer

Breast cancer is the leading cause of cancer death in women. It accounts for 15.5% of all cancer death worldwide [1]. The lowest age-standardized mortality rate for female breast cancer according to GLOBOCAN 2020 was observed in Eastern Asia (9.8 per 100,000 women). The 3 regions with the highest age-standardized mortality rate for female breast cancer were Micronesia/Polynesia (19.6 per 100,000 women), Western Africa (22.3 per 100,000 women), and Melanesia (27.5 per 100,000 women). In contrast to the incidence of female breast cancer, countries with a lower human development index have higher age-standardized mortality rates compared to regions with a higher human development index. Countries with a high to very high human development index have an age-standardized mortality rate of 12.8 per 100,000 women, while the rate is 15.0 for countries with a low to medium human development index [1]. For Germany the age-standardized mortality rate based on the European standard population is 22.8 per 100,000 women [39]. High age-standardized mortality rates in regions with a lower human development index, such as e.g. sub-Saharan Africa, are mainly attributable to a late diagnosis, because of insufficient screening programs. In addition, a lack of adequate treatment also has a major impact on the mortality rate [41]. Moreover, similar to cancer registry incidence data, most LMICs lack reliable nationally representative data on cause of death [42]. This hampers the comparability to countries with a high human development index.

1.1.5 Survival of female breast cancer

Survival of female breast cancer patients increased substantially over the past decades [43-48]. Although breast cancer is still the leading cause of cancer death among females [37], the 5-year relative survival exceeds 80% in many countries [4 49]. Among women with breast cancer in the United States (US), the 5-year relative survival increased from 74.0% during 1975 to 1979 to 88.5% during 2010 to 2015 [50]. According to the EUROCARE project, based on data of over 80 European cancer registries across 23 countries, breast cancer survival also increased significantly in Europe [45-47]. From 1990 to 1994 the 5-year relative survival for female breast cancer was 76% in Europe, with a higher survival in the Nordic countries, most southern countries and central European countries [44]. In eastern European countries survival ranged between 60%-70% in this period [44]. In 1995-1999 the 5-year relative survival of women diagnosed with breast cancer

increased to 79%, while inter-country differences in survival decreased [46]. In the latest report of EUROCARE the 5-year relative survival for female breast cancer further increased up to 82% for 2000-2007 in Europe [48]. This is also high compared to the 5-year relative survival for cancer overall in Europe (57%). For Germany, the 5-year absolute survival in 2018 was 81% and the 5-year relative survival was 89% for women with breast cancer. The 10-year relative survival was also relatively high with 85% [39]. The highest age-specific 5-year relative survival for female breast cancer in Germany in the period 2000-2007 was observed in the age group of 45-54 year old women. The lowest survival was observed in the age group of women who were older than 75 years at age at diagnosis [51].

The two main drivers for improved breast cancer prognosis are mammography screening and advancements in breast cancer treatment [52]. The stage of diagnosis is crucial in determining female breast cancer survival. Early detection through a mammography screening program can result in an earlier detection of breast cancer. Combined with an effective cancer treatment breast cancer specific mortality can be reduced [52]. Based on a simulation study on the impact of mammography screening and advances in therapy on breast cancer mortality in the US, a reduction in mortality by 37% (model range 27%-42%) was observed in 2000 compared to 1975. Of this 37% mammography screening contributed 44% (model range 35%-60%) and 56% (model range 39%-58%) were attributed to advancements in treatment [53].

1.2 Radiotherapy for female breast cancer

Therapy for breast cancer includes surgery and systemic treatments. Surgery can be differentiated into breast-conserving surgery and mastectomy. Systemic treatments include chemotherapy, endocrine therapy, and radiotherapy [23]. A cornerstone in breast cancer therapy, radiotherapy reduces local recurrences and breast cancer-related mortality [5 6 54]. Radiotherapy in breast cancer patients usually follows initial surgery and includes 5-6 weeks of postoperative whole breast irradiation [23 55]. This adjuvant radiotherapy is applied to eradicate clinically occult tumours deposited in the breast and also the chest wall or regional lymphatic drainage systems [56] to prevent local recurrence. The beneficial effect in patients with mastectomy as well as in patients with breast-conserving surgery was shown in two large meta-analyses of randomised clinical trials. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of individual data including 8,135 women [54]. The included women were treated between 1964 and 1986 in one of 22 clinical trials and followed up for 10 years for recurrence and until 2009 for mortality. For women with axillary dissection and one to three positive lymph nodes, radiotherapy reduced the risk for both recurrence (RR 0.68, 95% CI 0.57-0.82) and mortality (RR 0.80, 95% CI 0.67-0.95) [54]. The other large meta-analysis by the EBCTCG on patients with breast-conserving surgery included 10,801 women of 17 randomised clinical trials. Overall, radiotherapy was associated with a reduced 10-year risk for any first recurrence (absolute reduction 15.7%, 95% CI 13.7-17.7) [5]. The risk for breast cancer death was reduced by 3.8% (95% CI 1.6-6.0) in the first 15 years after diagnosis of breast cancer for women with radiotherapy. Although, the benefits of radiotherapy vary depending on characteristics of the patient, including age at diagnosis, grade, ER status, use of tamoxifen, and extent of surgery [5].

1.2.1 Radiotherapy treatment planning and techniques for female breast cancer

The delivery of radiotherapy for breast cancer changed substantially in the past 50 years. In older treatment periods, radiotherapy was mainly applied with Cobalt-60 machines and treatment planning was 2D. The design of the beam was based on physical examination or fluoroscopy [57 58]. This type of radiotherapy planning is referred to as conventional 2D radiotherapy. For conventional 2D radiotherapy usually a single-plane hand generated contour through the center of the breast was planned. The radiotherapy itself consisted of a single beam with boundaries delineated on orthogonal x-rays of the patients. The single beam could be applied from one to four directions [59]. The shaping of the beam was limited with this technique and simple square or rectangle beams were typically used. The low conformity of this technique resulted in high doses to adjacent healthy tissues or organs like the heart. This could lead to treatment side effects [60]. In addition, this could result in significant dose heterogeneity, especially for

women with larger breasts [61]. The introduction of computed tomography (CT) scans and more sophisticated and precise 3D treatment planning methods have improved the irradiation of the breast substantially [62]. 3D-conformal radiotherapy was proven as the preferred treatment planning in the late 1990s compared to conventional 2D radiotherapy [63]. Based on 3D images, the treatment of the tumour will be planned and the shapes of the radiation beam will be matched to the shape of the tumour. This enables avoiding the healthy surrounding tissue including the heart as much as possible. The 3D images are usually taken via one of the following imaging methods: CT, magnetic resonance imaging (MRI), positron emission tomography (PET), or PET-CT scan [64].

The common radiotherapy regime in 3D-conformal radiotherapy for breast cancer typically consists of a total dose of 50 Gray (Gy) in 25 fractions of 2 Gy over 5 weeks (conventional fractionation). This radiotherapy regime is based on the assumption that breast cancer is less sensitive to changes in the dose per each fraction compared to the dose-limiting healthy normal tissue [65]. Following this assumption, a sequence of small fractions (2 Gy) to a high total dose (50 Gy) spares the healthy tissue compared to the breast cancer tissue and therefore is beneficial [65]. During the 1980s an additional radiation boost dose was applied in nearly every patient after whole-breast irradiation. The boost is an extra dose given to the tumour bed and usually had a dose of 16 Gy [66]. The boost was given to help improve local control of recurrences. It comes at the cost of increased treatment costs and potential a worse cosmetic outcome [67]. For this reason, there has been a long ongoing debate about the clinical relevance of the use of a boost [66]. In a large randomized clinical trial overall survival and tumour recurrence and an additional boost of 16 Gy after whole breast radiation of 50 Gy in 5 weeks after breast-conserving surgery in 1989-1996 were assessed and reported for a 20-year follow-up [68]. The authors did not find a positive effect on long-term overall survival for an additional boost compared to no boost (hazard ratio (HR) 1.05, 95% CI 0.92-1.19). Nevertheless, they reported an improvement in local control in young patients and therefore conclude that an extra radiation boost can be avoided in most patients >60 years of age [68]. These results were recently supported by a comprehensive Cochrane systematic review [69].

1.2.2 Exposure of the heart in female breast cancer radiotherapy

Besides the clear benefits of radiotherapy, it does inevitably involve unwanted radiation to normal tissues. The esophagus, the lung and the heart are located near the clinical target volume of breast cancer radiotherapy. Their anatomical position makes them organs at risk (OAR) for adverse treatment effects [70]. Ionizing radiation to the heart due to radiotherapy for breast cancer can potentially lead to micro- and macrovascular damage. Microvascular damage can occur due to a decrease in capillary density, which can

result in a reduced degree of potential collateral flow in the heart. These changes on a microvascular level are mainly subclinical and appear soon after radiotherapy [7]. On a macrovascular level, radiotherapy might induce atherosclerosis of larger blood vessels. In contrast to the microvascular effects, this effect can take years to decades until it becomes clinically significant [7]. Evidence for an association of cardiac diseases and high-dose ionizing radiation is strong and has been investigated by numerous epidemiological studies [71 72]. In contrast, evidence for an association with low-dose radiation (<1 Gy) is less certain [73]. In terms of a pathophysiological mechanism biological plausibility for a radiation induced increased risk for heart diseases is established. Radiation may lead to oxidative stress, which then results in inflammatory cell infiltration. Followed by endothelial damage and fibrosis of the intima a hypercoagulable state can be observed, which then causes atherosclerosis in the coronary arteries [74 75].

Studies on the effects of radiotherapy in female breast cancer patients with long-term follow-up revealed an increased risk of cardiac death, which can be related to unwanted irradiation of the heart for older radiotherapy regimes [58 76]. The changes from conventional 2D radiotherapy to 3D-conformal radiotherapy resulted in a considerable reduction of the cardiac dose. In older regimes with conventional 2D treatment planning and Cobalt-60 breast cancer radiotherapy regimes and internal mammary chain radiation, the mean heart dose (MHD) for left-sided breast cancer was estimated to be 13.3 Gy and 4.6 Gy without internal mammary chain irradiation. For right-sided breast cancer the dose was estimated to be 2.3 with internal mammary chain irradiation and 1.2 Gy without [58]. In contrast, results of an overview by Taylor et al. [77] on 3D-conformal radiotherapy used in 2006 showed a decrease of the MHD to 2.3 Gy for left-sided irradiation and 1.5 Gy for right-sided irradiation [77]. Therefore, Taylor et al. [77] conclude that, due to newer techniques such as 3D-conformal radiotherapy clinicians were able to effectively reduce the cardiac dose.

Nevertheless, the heart remains exposed to ionizing radiation, also with 3D-conformal radiotherapy. The amount of exposure does not only depend on the irradiation technique, but also substantially on tumour laterality [77]. On average, radiotherapy for left-sided breast cancer is associated with higher doses to the heart compared to the right-sided breast cancer [78]. In a dosimetry study on dose distribution in the complete heart and functional heart regions, 769 female breast cancer patients in Germany were investigated. These breast cancer patients received irradiation during 1998-2008, with 3D-conformal radiotherapy, which is still the dominant approach compared to newer techniques, e.g., IMRT [78]. The average (median) volume weighted mean dose (DMEAN) was 4.6 Gy (3.7 Gy) for left-sided radiotherapy and 1.7 Gy (1.4 Gy) for right-sided radiotherapy [78]. Similar observations regarding tumour laterality and dose to the heart were reported in numerous single studies and summarized in two systematic reviews [79 80].

Another factor that needs to be taken into account is, that the heart is not a homogenous organ. Exposure to ionizing radiation through breast cancer radiotherapy to specific functional substructures of the heart, such as the coronary arteries, might be associated with characteristic late effects such as ischemic heart disease [81]. Ischemic heart disease was the predominant disease in previous international studies [76 82].This might indicate the coronary arteries as a critical structure for radiation induced cardiac late effects [81]. Part of the major coronary arteries is the left anterior descending (LAD) artery. The LAD has a crucial role in the perfusion of the myocardium. Therefore, myocardial necrosis and severe left ventricle impairment and congestive heart failure might follow the occlusion of the LAD [81]. In addition, the dose distribution during radiotherapy for breast cancer is not homogeneous. Small regions of the heart such as the LAD can be exposed to well over 20 Gy, even if the MHD is low [77]. For left-sided irradiated patients Taylor et al. [77] reported an average mean dose of 2.4 Gy for the complete heart, while the LAD was exposed to 7.6 Gy for 3D-conformal radiotherapy regimes in 2006 in the United Kingdom (UK). In a Swedish case-control study, including women treated with radiotherapy for breast cancer between 1992 and 2012 also high doses to the LAD were observed [83]. The median mean dose to the whole heart was 2.7 Gy in left-sided breast cancer patients. At the same time, it was 10.6 Gy for the LAD in these patients. For patients with right-sided breast cancer and radiotherapy the median MHD was 0.6 Gy and 1.6 Gy for the LAD [83]. In a study from Germany including patients with 3D-conformal radiotherapy several different heart structures were also investigated [78]. The left anterior heart wall (LAHW), including the left main coronary artery and the LAD received the highest doses. The average (median) exposure for the LAHW was 15.6 Gy (13.2 Gy) for left-sided irradiation of the breast and 1.3 Gy (1.2 Gy). Similar results regarding an increased exposure in the LAHW respectively the LAD was observed in an independent study by Taylor et al. [58], even though the treatment period included in Taylor et al. (1950s-1990s) is much older.

1.2.3 Recent developments in breast cancer radiotherapy

After the wide establishment of 3D-conformal radiotherapy in the late 1990s additional new developments in breast cancer radiotherapy, e.g., Intensity Modulated Radiation Therapy (IMRT), were introduced. IMRT was developed to further improve the target coverage of the tumour, dose homogeneity and reduction of toxicity in healthy tissues [63]. IMRT delivers highly conformal target doses and avoids high OAR doses. Nevertheless, it can include radiation beams passing through the heart resulting in a “low dose bath” [80]. In a recent multicenter prospective clinical trial effectiveness study 3D-conformal radiotherapy was compared to IMRT. IMRT was shown to be beneficial in terms of reducing acute toxicity, compared to 3D-conformal radiotherapy (odds ratio (OR) 0.64. 95% CI 0.45-0.91) [84]. Nevertheless, large epidemiological

studies on cardiac late effects on IMRT are not available yet. Further additional newer techniques that were included in today's radiotherapy regimes to reduce cardiac exposure are cardiac blocks, deep inspiration breath holds, prone techniques, [57] and volumetric modulated arc therapy (VMAT) [85]. A cardiac block implies a direct block of the heart in the radiation treatment field of the breast. The blocks are contoured based on the shape of the heart on CT images or directly on the radiation beam's eye views of digitally reconstructed radiographs [86]. Often a cardiac block is combined with deep inspiration breath hold techniques to further reduce the exposure to the heart, especially for IMRT. Doses to the heart can change due to respiratory motion resulting in an increased dose heterogeneity. Therefore, patients are guided to hold their breath while radiotherapy is delivered, which results in the heart being pushed downside and away from the radiotherapy field [87]. Another patient related technique to reduce exposure to the heart is called prone technique. Conventionally, radiotherapy is applied while the patient is in supine position [88]. Radiotherapy applied to a patient in prone position takes advantage of gravity. In prone position the breast will be pulled away from the chest wall [86]. Although, it is more challenging to immobilize patients in prone positions and reproduce the patients position setup throughout the treatment [88]. One other technique to reduce exposure to the heart due to radiotherapy for breast cancer is VMAT. Radiation dose is applied continuously as the treatment machine rotates around the patient. First introduced in 2007, VMAT is a so called arc-based or rotational therapy, as the basic concept of VMAT is the delivery of radiation from a continuous rotation of the radiation source. This allows the application of radiation to the patient from full 360° beam angle [89], with the potential downside of a "low dose bath" of healthy tissue [90].

Several clinical trials investigated the use of hypofractionated whole-breast irradiation as a newer alternative to the conventional fractionation, namely The Standardisation of Breast Radiotherapy (START) [65 91 92] and others [93-95]. Hypofractionation includes higher but fewer single doses in combination with a reduced total dose. The entire breast is treated with 2.5 Gy-3.20 Gy in 13-15 fractions over a period of 3-5 weeks, resulting in 39 Gy-42.5 Gy in total [55 65]. The combination of shorter treatment course, decreased total dose and number of fractions results in lower costs and an increased patient convenience [65]. Several randomized trials in women with early-stage breast cancer and breast-conserving surgery [65 91-93 96] showed that hypofractionation was not inferior to the conventional fractionation and could offer similar rates of tumour control and normal tissue damage. This means that breast cancer tissue might be just as sensitive to fraction size as the dose-limiting healthy tissue [95].

1.2.4 German S3 guideline on radiotherapy of breast cancer

With regard to radiotherapy for breast cancer in Germany the official S3 guideline is an important source of information for evidence-based therapy decision-making for clinicians [97]. For patients with an invasive carcinoma of the breast, the S3 guideline generally recommends radiotherapy after breast-conserving surgery. However, for patients with a clearly limited life expectancy, which is mentioned as less than 10 years, and a small (pT1), nodal-negative (pN0), hormone receptor-positive HER2-negative tumour with tumour-free surgical margins endocrine therapy and radiotherapy can be omitted [97]. The S3 guideline further recommends the application of moderate hypofractionation with a total dose of approximately 40 Gy in 15-16 fractions over a period of 3-5 weeks. Alternatively, conventional fractionation can be applied. Because of the previously mentioned benefits of hypofractionation, the recommendation for hypofractionation currently applies generally to all adjuvant radiotherapy of breast cancer without affected lymphatic duct. However, if the lymphatic ducts should be irradiated, the guidelines recommends conventional fractionation [97]. Regarding a boost, the application of an additional boost to the tumour bed is recommended for all patients ≤50 years of age. For patients older than 50 years, an additional boost should only be applied in patients with a high risk for recurrences (e.g. HER2+ or triple negative) [97].

1.3 Epidemiological studies on cardiac late effects in female breast cancer patients with radiotherapy

Due to mammography screening and effective adjuvant therapy survival of female breast cancer patients increased substantially [2 3]. At the same time, the demographic transition towards an older population [98] increases the risk group for breast cancer. Taken together, both developments lead to an expanding population at risk for long-term health effects in breast cancer patients. This gives rise to an increasing interest in cardiac late effects in female breast cancer patients [99 100]. Cardiac diseases are already frequent in the general population, and thus frequent in breast cancer patients, as well. In addition, anthracyclines, the most common class of chemotherapeutic agents, as well as radiation exposure to the heart due to radiotherapy may be cardiotoxic [101 102]. Because of the high baseline prevalence of cardiac disease, even small radiotherapy-induced increases in cardiac risk in breast cancer patients can cause many additional affected patients [103]. Cardiac disease accounts for up to 10.4% of all deaths among breast cancer patients [104]. Therefore, cardiac late effects in the context of radiotherapy in breast cancer patients is a topic of interest in many epidemiological studies. Epidemiological research in this area can be based on studies using tumour laterality as a surrogate measure for the level of radiation exposure to the heart (Section 1.3.1), or on studies with individual heart dosimetry enabling for dose-response analysis (Section 1.3.2).

1.3.1 Studies on tumour laterality

In a number of epidemiological studies on radiotherapy in breast cancer patients and risk for cardiac late effects tumour laterality is used as a proxy for radiation exposure to the heart. In older cohorts of the era of conventional 2D radiotherapy no CT slides were available. Even when 3D-imaging data is obtainable in newer cohorts, retrospectively assessing individual heart dosimetry is time consuming. Usually manually contouring of each individual heart is needed, which is resource-intensive and is not part of the initial radiotherapy treatment planning routine [105]. Therefore, tumour laterality is often used as a dose proxy for radiation exposure to the heart. This approach reflects the evidence that patients with left-sided breast cancer have higher heart-exposure from radiotherapy compared to patients with breast cancer on the right side due to the anatomical position of the heart in the mediastinum. The use of laterality enables an unbiased analysis in a quasi-randomized study design. Since tumour laterality is mostly random, unknown confounders are distributed equally in both groups, left-sided and right-sided breast cancer patients [103]. As a possible alternative proxy for radiation exposure to the heart, a straightforward comparison of patients with radiotherapy and patients without radiotherapy would also be theoretically conceivable. However, the comparison of patients with radiotherapy and without radiotherapy suffers from indication

bias and self-selection effects outside from randomized trials as it is associated with disease characteristics, patient characteristics, and patient preferences [106]. Therefore, comparing women with radiotherapy and women without radiotherapy for breast cancer in order to assess a potential increased risk for cardiac late effects due to ionizing radiation in epidemiological studies is hampered and tumour laterality is considered a more robust comparison [107].

There are several epidemiological studies that analyzed the risk of radiotherapy for cardiac mortality based on tumour laterality [103 106 108-117]. In general, the results of these studies are not completely consistent, but there is arguably a pattern driven by the treatment period. Studies that included patients who received radiotherapy in earlier treatment periods [108 109] tend to report increased risks for cardiac mortality in left-sided breast cancer patients with radiotherapy compared to right-sided breast cancer patients. Darby et al. [108] identified a significantly increased risk in women diagnosed between 1973-1982 in the US. The highest mortality ratio for cardiac death was identified in subgroups with long-term follow-up of 10-14 years (mortality ratio (MR) 1.42, 95% CI 1.11-1.82) and a follow-up of ≥15 years (MR 1.58, 95% CI 1.29-1.95) [108]. On the contrary, in the same study no significant increased risk for cardiac mortality was observed in women with left-sided radiotherapy compared to women with right-sided radiotherapy treated between 1983-1992 and 1993-2001 [108]. The authors argue that this might be due to lower cardiac doses in more recent radiotherapy techniques. In addition, Darby et al. [108] emphasize the need for a longer follow-up. Especially, because the follow-up for the treatment period of 1993-2001 is relatively short and analysis of long-term cardiac mortality was therefore only possible to a limited extend for this strata. Likewise, in an extension of the study by Darby et al. [108] with additional follow-up until 2009, Henson et al. [109] confirmed the findings by Darby et al. [108]. They identified a significant increase in risk for cardiac mortality in left-sided vs. right-sided breast cancer patients after radiotherapy for the years 1973-1980 with the highest risk in the strata with the longest follow-up of more than 20 years (MR 1.90, 95% CI 1.52-2.37). For more recent treatment periods again no increased risk was observed. Although, the follow-up for the latest time period strata of 2003-2008 was still short, with less than 10 years (MR 1.00, 95% 1.03-1.14) [109]. Studies that mainly included women with contemporary techniques in more recent years are consistent with the findings of Darby et al. [108] and Henson et al. [109] regarding no to little evidence for an increased mortality risk based on tumour laterality and radiotherapy. This is also supported by studies that primarily focused on patients treated with contemporary techniques such as 3D-conformal radiotherapy in breast cancer patients considering laterality as a proxy for radiation dose to the heart. Rutter et al. [110] included over 344,000 patients through the National Cancer Database in the US. Patients were treated from 1998-2006 and risk for mortality was identical for left-sided and right-sided cancers (HR 1.003, 95%

CI 0.973-1.032). Although, this analysis was on overall mortality and not specific on cardiac mortality. In addition, the follow-up with a median of 6.04 years is short. Especially in the light of the earlier findings by Darby et al. [108] and Henson et al. [109], indicating an increased risk for cardiac morality in the strata with longer follow-up. Nevertheless, in a sensitivity analysis restricted to patients with a follow-up of at least 10 years, the result did not differ (HR 0.938. 95% CI 0.855-1.029) compared to the main results. The findings of no increased cardiac mortality risk in left-sided breast cancer patients vs. right-sided breast cancer patients after radiotherapy are further supported by studies of McGale et al. [106], Bouchardy et al. [112], Boero et al. [114], Li et al. [113], and Henson et al. [117]. All these studies discuss their findings in regard to their follow-up that might be too short to identify harmful effects of radiotherapy on cardiac mortality. For this reason, it can be noted that studies with sufficiently long follow-up are still lacking when investigating the effect of modern 3D-conformal radiotherapy. The issue of a limited follow-up was also discussed in the so far only two studies from Germany on cardiac mortality in breast cancer patients after treatment with modern 3D-conformal radiotherapy between 2001-2005 [115] and 1998-2008 [116]. The main analysis of Obi et al. [115] of the MARIEplus cohort was focused on the comparison of women with radiotherapy vs. women without radiotherapy. In a sensitivity analysis on tumour laterality including 1,200 women with a left-sided tumour and 1,159 women with a right-sided tumour no increased risk for cardiac mortality was observed. Although, the authors did not report the risk estimates [115]. In Merzenich et al. [116] the HR for cardiac mortality was 0.94 (95% CI 0.64-1.38) for left-sided versus right-sided tumours based on over 9,000 patients with 3D-conformal radiotherapy in 1998-2008. With a median follow-up of 6.5 years and a maximum follow-up of 14 years Merzenich et al. [116] also discussed the follow-up as possibly being too short to detect long-term cardiac mortality reliably and therefore recommended a longer follow-up. [116].

Beside studies on cardiac mortality, there are also studies focusing on the risk of cardiac morbidity and tumour laterality in female breast cancer patients who received radiotherapy [103 106 114 118-121]. Contrary to studies on cardiac mortality, studies on cardiac morbidity revealed increased risks for both older and more recent therapy regimes. In a large cohort study by Boekel et al. [118] 70,209 female breast cancer patients from the Netherlands were included. For the treatment period between 1989 and 2005 they identified a slightly increased risk for any cardiovascular event for left-sided vs. right-sided radiotherapy after mastectomy (subdistribution hazard ratio (sHR) 1.19, 95% CI 1.04-1.36), including ischemic heart diseases, valvular heart disease and congestive heart failure [118]. Comparable results were reported in a study on approximately 20,000 early-stage breast cancer patients in Denmark treated from 1977-2005 [119]. For this study an increased incidence risk ratio (IRR) of 1.11 (95% CI 1.03-1.20) for all heart diseases were estimated

comparing left-sided vs. right-sided irradiated patients. This effect was present in both older treatment periods, i.e., 1977-1989 (IRR 1.24, 95% CI 1.07-1.43) and more recent treatment periods including the years 2001-2005 (IRR 1.15, 95% CI 1.01-1.31). In stratified analyses for type of surgery the increased risk was statistically significant for patients who underwent mastectomy (IRR 1.13, 95% CI 1.01-1.26), but not for breast-conserving surgery (IRR 1.10, 95% 0.99-1.22) [119]. Another study from Denmark also identified similar risks for cardiac disease in both older treatment periods from 1976-1989 in left-sided vs. right-sided irradiated women (IRR 1.08, 95% CI 1.01-1.15) and more recent treatment periods from 1990 onwards (IRR 1.09, 95% CI 1.00-1.19) [106].

On the other hand, there is also a number of studies that did not observe a significant increased risk for long-term cardiac morbidity after radiotherapy in female breast cancer patients [103 114 120 121]. In a study based on the Surveillance, Epidemiology, and End Results (SEER)-Medicine database including patients treated in 2000-2009 no significant increased risk for cardiac morbidities was observed in left-sided vs right-sided irradiated patients [114]. Cardiac morbidities included myocardial infarctions (sHR 1.05, 95% CI 0.98-1.13), coronary artery disease (sHR 1.04, 95% CI 1.00-1.08), dysrhythmias (sHR 1.01, 95% CI 0.98-1.04), and congestive heart failure (sHR 0.97, 95% CI 0.92-1.04) [114]. For cardiovascular diseases, no statistically significant increased risk was identified in a study on 4,333 Korean breast cancer survivor treated with radiotherapy in 1996-2010 following breast-conserving surgery comparing left-sided and right-sided tumour laterality (HR 1.21, 95% CI 0.75-1.95) [120]. However, another large Danish study on early breast cancer patients reported a statistically increased risk for left-sided irradiated patients for the treatment period 1999-2007 (IRR 1.44, 95% CI 1.07-1.94), but not for patients treated between 2008-2016 (IRR 0.90, 95% CI 0.69-1.16) [121]. There is also one study from Germany on cardiac morbidity in breast cancer survivor with radiotherapy using tumour laterality as a surrogate for cardiac dose [103]. Based on a self-administered questionnaire cardiac morbidity was assessed in 4,434 women with radiotherapy for breast cancer in 1998-2008. No significant association of tumour laterality and cardiac morbidity after a median follow-up of 8.3 years was observed (HR 1.07, 95% CI 0.89-1.29) [103].

1.3.2 Studies on dose-response relationship

Using laterality as a proxy for radiation exposure to the heart is sub-optimal compared to quantitative heart dosimetry as the heart is not a homogenous organ and consists of different substructures (Section 1.2.2). There also is considerable variability in radiation exposure to the heart and its different functional substructures during radiotherapy [78]. Therefore, a more precise assessment of cardiac morbidity and cardiac mortality in female breast cancer patients after radiotherapy should be based on the dose to the

heart and related functional substructures [122]. This also enables to estimate a potential dose-response trend and derive information about the particular shape of a dose-response curve. However, compared to the large body of evidence on tumour laterality and cardiac late effects in breast cancer patients, studies using dose estimates are sparse [76 82 122 123] and for Germany so far non-existent.

In a landmark study, Darby et al. [76] investigated the association between long-term major cardiac events (including myocardial infarction, coronary revascularization and death from ischemic heart disease) and the heart dose from radiotherapy in breast cancer patients. They conducted a case-control study, involving 2,169 women from Sweden and Denmark for the treatment period 1958-2001. Estimated exposure to the heart from radiotherapy in breast cancer patients was associated with an increased risk for long-term major cardiac events by 7.4% per Gy (95% CI 2.9%-14.5%) MHD with no apparent threshold [76]. During the treatment period in this study conventional 2D radiotherapy was the prevailing treatment. Individual radiotherapy charts, diagrams and photographs of the treatment field for each patient were obtained to retrospectively simulate the radiotherapy regime applied to each woman. On a CT scan of a woman with typical anatomy the individual information of the dose charts and other available information was applied. Based on dose-volume histograms doses to the heart were reconstructed [76]. Lately, one study on 3D-conformal radiotherapy have been published. Van den Bogaard et al. [82] reported a 16.5% increase in cumulative incidence (95% CI 0.6%-35.5%) per Gy MHD for long-term cardiac major coronary events (based on the same outcome definition as Darby et al. [76]). Although, in this study a more recent treatment period is observed (2005-2008), the analysis is based on only 30 cases. This considerably limits the reliability of the analyses, which is also expressed by the wide confidence interval of the risk estimates in this study. There are two more case-control studies on this subject, however, again on older treatment periods. One is from the Netherlands [123] and the other is from Denmark [122]. In the study from the Netherlands including patients mostly treated before 2000 in the period of 1970-2009 an increased risk of 6.4% (95% CI 1.3% 16.0%) per 1 Gy MHD for myocardial infarctions was observed [123]. In the Danish study a 19% increase per 1 Gy MHD (95% CI 1%-63%) for long-term major cardiac coronary events (using the definition of Darby et al. [76]) was reported. This study does also include patients with older treatment regimens starting from 1977 to 2005. Therefore, today data from studies on contemporary 3D-conformal radiotherapy based on a sufficient number of cases and precise dosimetry is sparse, and completely missing for Germany.

The presented international studies on cardiac late effects after radiotherapy in breast cancer patients using individual cardiac radiation doses are mainly using the mean dose to the complete heart to characterize cardiac radiation exposure [76 82 122 123]. Nevertheless, using the mean dose to the complete

heart has limitations. The heart is not a homogeneous organ (Section 1.2.2). Therefore, damage to specific functional substructures of the heart, such as the coronary arteries, including the LAD, might be associated with characteristic late effects such as ischemic heart disease [81]. Ischemic heart disease was the predominant disease in the previous international studies [76 82], which might indicate the coronary arteries as a critical structure for radiation induced cardiac late effects [81]. This raises the open question if radiation exposure to the LAD is a better predictor for cardiac late effects compared to the mean exposure of the complete heart. In addition, alternative dose metrics for risk assessment of cardiac late-effects after breast cancer radiotherapy are topic of ongoing research and discussion [124]. Recently, van den Bogaard et al. [82] showed that the volume of the left ventricle receiving ≥5 Gy (V5Gy) might be a better predictor for long-term major cardiac coronary events (outcome definition of Darby et al. [76]). They identified a small but significantly increased HR of 1.016 (95% CI 1.002-1.030) for V5Gy to the left ventricle. Although, the study is based on only 30 cases. This hampers the reliability and robustness of the model used by van den Bogaard et al. [82]. Jacobse et al. [123] also looked at V5Gy as an alternative dose metric to the mean dose to the complete heart. They observed a RR of 2.02 (95% 1.43-2.85) for myocardial infarction for ≥30% of the heart receiving a dose of ≥5 Gy (V5Gy) compared to the reference category of <10% of the heart with V5Gy. However, the dosimetry done in the study of Jacobse et al. [123] is subject to sources of uncertainty regarding the cardiac dose. As most included women in this study were treated before the era of 3D-conformal radiotherapy (>90% of included patients were treated before 2000) individual dosimetry data through CT planning scans was not available. Therefore, solely based on reconstructed radiotherapy regimes the exposure to the heart was estimated on the scan of a typical CT and not on individual scans for each patient. This can lead to different dose estimates compared to the actual dose because of inter-patient differences in anatomy [123].

1.4 Scope of this thesis

This cumulative PhD-thesis is based on two internationally published epidemiological articles that are targeting important questions on cardiac late effects in female breast cancer patients after 3D-conformal radiotherapy. In particular, the articles provide insight in risk for cardiac late effects in the German setting for contemporary radiotherapy regimes with long-term follow-up and individual dosimetry. No results from studies with similar scope and scale have been previously reported. Thus, the two articles' contribution are especially valuable to inform medical decision making in the application of radiotherapy. The main questions and scope of this thesis are outlined below.

Article I: Cardiac late effects after modern 3D-conformal radiotherapy in breast cancer patients: a retrospective cohort study in Germany (ESCaRa) (Section 3)

In this article the following two research questions are targeted:

- Is the risk for long-term cardiac mortality increased in women with 3D-conformal radiotherapy for left-sided breast cancer compared to women with right-sided breast cancer?

- Is the risk for long-term cardiac morbidity increased in women with 3D-conformal radiotherapy for left-sided breast cancer compared to women with right-sided breast cancer?

In brief, to answer these research questions data of a cohort of 11,982 female breast cancer patients treated between 1998 and 2008 in Germany was used (ESCaRa cohort, Section 2.1). Outcome data was obtained based on a mortality follow-up until June 2018 and a morbidity follow-up due to a questionnaire in 2014 and 2019 on cardiac morbidity after breast cancer treatment. To assess the effect of 3D-conformal radiotherapy for breast cancer on cardiac mortality and cardiac morbidity, tumour laterality was used as a proxy for radiation exposure to the heart. Multivariable cox proportional hazards regression analysis was performed to assess the association of cardiac mortality and cardiac morbidity with tumour laterality. Potential confounders including age at diagnosis, year of diagnosis, cardiac history, chemotherapy, endocrine therapy and BMI were included in the model. For missing information on chemotherapy, endocrine therapy and BMI multiple imputation using fully conditional specification method, assuming data missing at random, was applied. To assess survival after radiotherapy Kaplan-Meier Method was used. To compare survival of left-sided vs. right-sided radiotherapy Mantel-Haenzel (log-rank test) was applied.

Article I

Merzenich H, **Baaken D**, Schmidt M, Bekes I, Schwentner L, Janni W, Wöckel A, Bartkowiak D, Wiegel T, Blettner M, Wollschläger D, Schmidberger H. (2022). Cardiac late effects after modern 3D-conformal radiotherapy in breast cancer patients: a retrospective cohort study in Germany (ESCaRa). *Breast Cancer Research and Treatment* 191: 147-157. https://doi.org/10.1007/s10549-021-06412-3

Article II: A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany (Section 4)

This article addresses the following two research questions:

- Is the risk for long-term cardiac events associated with mean dose from 3D-conformal radiotherapy for female breast cancer to the complete heart or the left anterior heart wall (LAHW) including the left anterior (LAD) coronary artery descending?

- Is the risk for long-term cardiac events associated with the dose-volume metric V5Gy from 3D-conformal radiotherapy for female breast cancer to the complete heart or the left anterior heart wall (LAHW) including the left anterior (LAD) coronary artery descending?

In a cohort of 11,928 women (ESCaRa cohort, Section 2.1) treated with 3D-conformal radiotherapy for breast cancer in Germany between 1998-2008, 494 cases who subsequently developed a cardiac event after therapy were identified. A cardiac event was defined as either death from a cardiac cause such as a cardiac infarction or the diagnosis of a cardiac disease such as congestive heart failure. Within a nested case-control approach the 494 cases were matched to 988 controls using 1:2 incidence-density sampling with replacement. Independently from the nested case-control study, a sample of 1,353 women from the ESCaRa cohort representative in terms of age and tumour laterality was selected to estimate individual heart dosimetry (Section 2.4). For 91 cases and 182 corresponding controls individually estimated volume weighted mean dose (DMEAN) and V5Gy of the complete heart and the left anterior heart wall could be extracted from the independent dosimetry sample. For the rest without individual dosimetry, doses were imputed based on a prediction model. Separate multivariable conditional logistic regression models were used to assess the association of radiation to the complete heart and the left anterior heart wall with cardiac events. Further, analyses for V5Gy as an alternative dose metric were carried out.

Article II

Baaken D, Merzenich H, Schmidt M, Bekes I, Schwentner L, Janni W, Wöckel A, Meyer M, Mose S, Merz T, Ghilescu V, Renner J, Bartkowiak D, Wiegel T, Blettner M, Schmidberger H, Wollschläger D. (2022). A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany. *The Breast* 65: 1-7.
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This cumulative PhD-thesis is structured as follows: First, the ESCaRa-Study (Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients) is presented in Section 2, as this study forms the basis for the analyses of this work and the related publications. Section 3 and Section 4 consist of the two articles of this thesis, preceded by some preliminaries that motivate each article. Finally, in Section 5 a joint discussion of the two articles conclude the results of this thesis.

2 The ESCaRa-Study

The ESCaRa-Study is a retrospective multicenter cohort study with the aim to assess the long-term risk for cardiac mortality and cardiac morbidity in female breast cancer patients in Germany treated with 3D-conformal radiotherapy in 1998-2008. The ESCaRa-Study is an extension to the PASSOS Heart Study (Personalized assessment of late health risks after radiation exposure for optimization of medical application in medicine network) [103 116].

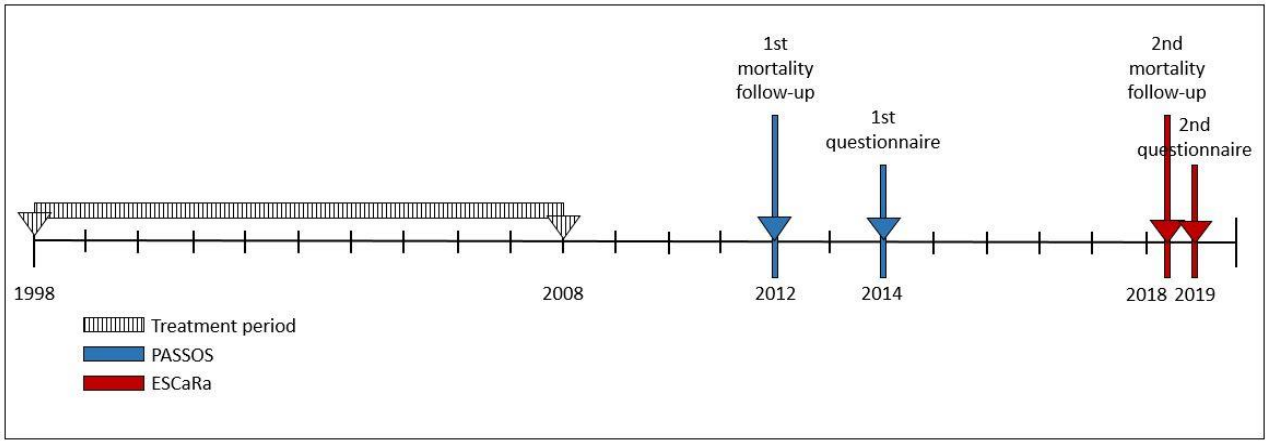

Figure 1: ESCaRa-Study profile

2.1 Study population

The cohort of the ESCaRa-Study consists of 11,982 female breast cancer patients with cancer treatment between 01/1998 and 12/2008 (Figure 1). Treatment was carried out at Mainz University Medical Center's Department of Obstetrics and Gynaecology, at the Ulm University Hospital's Department of Gynaecology and Obestrics, or at one of 16 certified breast cancer centers in the vicinity of Ulm. Inclusion criteria were a histologically confirmed primary and locoregional breast cancer, either an invasive carcinoma or carcinoma in situ. Women with a primary metastatic disease or bilateral breast cancer were excluded. Medical records were retrieved to abstract individual clinical data on breast cancer disease, therapy, and comorbidities during the PASSOS Heart Study. Information on treatment data included type of surgery, adjuvant systematic chemotherapy, adjuvant endocrine therapy, and detailed information on administered adjuvant radiotherapy. In a mortality follow-up data on vital status and cause of death was assessed until 06/2018 (Section 2.2) (Figure 1). Via a self-administered questionnaire in 2014 and 2019, information on socio-demographic variables, lifestyle factors and incident cardiac events (cardiac

morbidity) was collected (Section 2.3) (Figure 1). The patients received 3D-conformal radiotherapy in one of the ESCaRa-Study centers at the University Medical Center in Mainz, Ulm or one 16 collaborative partner clinics including information on tumour laterality of radiotherapy for all patients. For a selected dosimetry sample of 1,353 patients from the ESCaRa-Study individual heart dosimetry was carried out retrospectively (Section 2.4).

The ESCaRa-Study has been approved by the Ethics Committee of Rhineland-Palatinate, Mainz and the Ethics Committee of the University of Ulm. Use of patients' hospital records and the conduct of a mortality follow-up without written informed consent for the entire cohort of the ESCaRa-Study was approved by the data protection officer of Rhineland-Palatinate. For the self-administered questionnaire, individual informed consent was obtained.

2.2 Mortality follow-up

To receive information on vital status and cause of death, including cardiac death, individual mortality follow-up was conducted for all 11,982 patients. The corresponding compulsory population registries of the municipalities of the last known residences were contacted regarding vital status. Death certificates were obtained via the local health authorities of the place of death. The underlying cause of death was coded based on ICD-10. In an initial mortality follow-up in the PASSOS Heart Study vital status and cause of death were assessed until December 2012, resulting in a median follow-up of 6.5 years with a maximum of 14 years [116]. For the ESCaRa-Study the follow-up was extended until 06/2018, resulting in an additional 5.5 years of systematic mortality follow-up (Figure 1).

2.3 Self-administered questionnaire

During the PASSOS Heart study a first questionnaire was mailed in 2014 to female breast cancer patients who were treated in one of the study clinics and were reported alive [103] (Figure 1). The initial questionnaire included 25 questions on socio-demographic variables, clinical diagnosis of cardiac diseases prior to the breast cancer treatment, potential modifiable lifestyle factors for cardiac disease, cancer therapy, and second primary cancers. Patients who refused to participate in the extensive questionnaire were asked to fill out a short form with questions of incident cardiac events after breast cancer treatment. In 2019, a second questionnaire was send out for the ESCaRa-Study to patients that participated in first questionnaire

in 2014, were reported alive and gave permission for a second contact during the PASSOS Heart Study. The questionnaire in 2019 was identical to the short form questionnaire in 2014 (Appendix A, S1).

2.4 Retrospective dosimetry

Among the 11,982 female breast cancer patients included in the cohort of the ESCaRa-Study 9,057 women had radiotherapy treatment during 1998-2008 in one of the ESCaRa-Study clinics (Figure 1). Most patients (>75%) with radiotherapy were treated after 2000 with slightly more patients treated for a left-sided tumour (51.04%) than a right-sided tumour (48.96%). All women with radiotherapy in the cohort were treated with 3D-conformal radiotherapy based on image slices from static CT without contrast enhancement [105]. Standard treatment planning contained two tangential fields of 6 megavolt (MV) photons. Supplementary, photons of 10 MV were used as a field-in-field application. Attending physicians at the ESCaRa-Study clinics determined the tangential field boarders and angles to encompass the whole palpable breast. For patients with mastectomy, the lateral field border was defined as the mid-axillary line, and the medial field border as the midline [105].

A total radiation dose of 50 Gy was typically applied to the planning target volume. The total dose was administered in 25 fractions with five fractions per week. To cover the internal mammary lymph nodes, radiotherapy could also include a supraclavicular field as well as an anterior-posterior parasternal field optionally [116]. Patients who underwent breast-conserving surgery usually received an additional boost of 10 Gy to the tumour bed. Radiotherapy was applied with the patients being in a supine position, immobilized on a breast board with both hands above the head [105]. Additional techniques that are included in today's radiotherapy regimes to reduce cardiac exposure such as cardiac blocks, deep inspiration breath holds, and prone techniques were not applied to the ESCaRa-Study patients in 1998-2008. Neither were IMRT, VMAT or hypofractionation part of the standard radiotherapy treatment regimen for the ESCaRa-Study patients at that time.

From the complete cohort of the ESCaRa-Study a dosimetry sample of 1,353 patients for individual heart dosimetry was drawn randomly. To ensure representativeness of the drawn sample for the complete cohort of the ESCaRa-Study, age at diagnosis, tumour laterality, and treatment center (Mainz, Ulm, or one of the 16 partner clinics in the vicinity of Ulm) were taken into account for sampling. Retrospective dosimetry was based on individual CT scans from initial treatment planning and comprehensive information on the implemented radiotherapy fields. To receive individual dose-volume histograms for all patients in the dosimetry sample a contouring atlas was applied [125]. Contouring substructures were defined

as geometrical surrogate volumes of anatomical structures, including the complete heart and the LAHW. The complete heart was defined in accordance to the Radiation Therapy Oncology Group definition for radiotherapy in breast cancer. The LAHW includes the LAD. Cumulative dose-volume histograms for each patient of the dosimetry sample and heart structures were exported from the treatment planning software Eclipse to the statistical environment R [78 125]. Based on these dose-volume histograms the volume-weighted mean dose (DMEAN) and the relative volume with a dose of ≥5Gy (V5Gy) for each patient of the dosimetry sample was calculated [78].

3 Article I: Cardiac late effects after modern 3D-conformal radiotherapy in breast cancer patients: a retrospective cohort study in Germany (ESCaRa)

3.1 Preliminaries Article I

As outlined (Section 1.3.1), studies on modern 3D-conformal radiotherapy with sufficiently long follow-up to investigate cardiac late effects are missing, especially for female breast cancer patients in Germany. A recent systematic review showed, that there is considerable heterogeneity among countries in Europe (p=.004) with MHD ranging from 1.8 Gy to 9.5 Gy [79]. Therefore, regional differences in radiotherapy practices and speed of implementation of newer techniques might be present, suggesting the importance of country-specific assessment of cardiac risk in breast cancer patients with radiotherapy.

Article I reports results for cardiac mortality, cardiac morbidity, and overall survival based on an extended mortality and morbidity follow-up of the ESCaRa-Study for female breast cancer patients with contemporary 3D-conformal radiotherapy received during 1998-2008 in Germany. The extended follow-up allows for a more accurate estimation of long-term cardiac effects after radiotherapy in female breast cancer patients. In addition, an increased number of cases enables for more complex regression models and finer stratified analyses incorporating e.g. duration of follow-up. This makes Article I an important contribution to the body of evidence on cardiac late effects after modern radiotherapy in female breast cancer patients based on a large cohort with comparable long follow-up, which is still sparse internationally and unique for Germany.

3.2 Article I

Merzenich H, **Baaken D**, Schmidt M, Bekes I, Schwentner L, Janni W, Wöckel A, Bartkowiak D, Wiegel T, Blettner M, Wollschläger D, Schmidberger H. (2022). Cardiac late effects after modern 3D-conformal radiotherapy in breast cancer patients: a retrospective cohort study in Germany (ESCaRa). *Breast Cancer Research and Treatment* 191: 147-157.
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EPIDEMIOLOGY

Cardiac late effects after modern 3D-conformal radiotherapy in breast cancer patients: a retrospective cohort study in Germany (ESCaRa)

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Abstract

Purpose Radiotherapy (RT) was identified as a risk factor for long-term cardiac effects in breast cancer patients treated until the 1990s. However, modern techniques reduce radiation exposure of the heart, but some exposure remains unavoidable. In a retrospective cohort study, we investigated cardiac mortality and morbidity of breast cancer survivors treated with recent RT in Germany.

Methods A total of 11,982 breast cancer patients treated between 1998 and 2008 were included. A mortality follow-up was conducted until 06/2018. In order to assess cardiac morbidity occurring after breast cancer treatment, a questionnaire was sent out in 2014 and 2019. The effect of breast cancer laterality on cardiac mortality and morbidity was investigated as a proxy for radiation exposure. We used Cox Proportional Hazards regression analysis, taking potential confounders into account.

Results After a median follow-up time of 11.1 years, there was no significant association of tumor laterality with cardiac mortality in irradiated patients (hazard ratio (HR) for left-sided versus right-sided tumor 1.09; 95% confidence interval (CI) 0.85–1.41). Furthermore, tumor laterality was not identified as a significant risk factor for cardiac morbidity (HR = 1.05; 95%CI 0.88–1.25).

Conclusions Even though RT for left-sided breast cancer on average incurs higher radiation dose to the heart than RT for right-sided tumors, we found no evidence that laterality is a strong risk factor for cardiac disease after contemporary RT. However, larger sample sizes, longer follow-up, detailed information on individual risk factors and heart dose are needed to assess clinically manifest late effects of current cancer therapy.

Keywords Breast cancer · 3D-conformal radiotherapy · Cardiac mortality · Cardiac morbidity · Cohort study · Survival

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Abbreviations

BMI	Body mass index
CIS	Carcinoma in situ
CI	Confidence interval
Gy	Gray
ICD	International classification of diseases
HR	Hazard ratio
NYHA	New York heart association
RT	Radiotherapy
SI	Supplementary information

Introduction

Annually more than two million women are diagnosed with breast cancer [1]. The prognosis of breast cancer has improved substantially. Currently the relative 5-year

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survival exceeds 80% in many countries [2], partly due to earlier diagnosis and adjuvant therapies. Radiotherapy (RT) is an important component of breast cancer treatment and reduces local recurrence and breast cancer mortality after breast conserving surgery [3]. Despite the benefit, long-term cardiac side effects related to RT are of clinical concern. Radiation-induced cardiotoxicity is caused by lesions of the microvasculature or by conduction abnormalities and arrhythmias related to autonomic dysfunction [4–6].

Observational studies have shown that breast cancer patients with RT for left-sided tumors had higher risk for coronary heart disease and cardiac mortality compared to those with right-sided RT [7]. A review [8] based on studies from 28 countries reported a mean dose to the whole heart of 5.4 Gray (Gy) on average for left-sided breast cancer and 3.3 Gy for right-sided breast cancer. Assuming that tumor laterality is almost completely random, observational studies comparing cardiac outcomes in women irradiated for left- versus right-sided breast cancer may reveal the effect of higher vs. lower radiation doses [9].

Clinical manifestations of cardiac outcomes after RT in breast cancer patients seem to decrease with each decade [7, 10]. Beginning in the late 1980s [11], advances in RT including techniques such as 3D-treatment planning, and respiratory gating have substantially reduced cardiac dose. However, even modern RT may cause a cardiac risk [12] since the heart remains exposed, mainly depending on tumor laterality and individual anatomical risk factors [8, 12]. Studies with detailed information about individual cardiac dose have shown a linear dose–response relationship [13, 14].

Assessing the long-term cardiac risk of patients treated with modern RT requires decades of follow-up. The risk for coronary heart disease started to increase within the first decade after breast cancer and continued into the following decades [13]. With a low number of events and the competing mortality risk from breast cancer, observational studies require large sample sizes [10]. Furthermore, accounting for individual patient risk factors requires detailed data on cardiovascular comorbidity. Breast cancer patients can also receive anthracyclines and other cardiotoxic drugs whose effects on cardiovascular outcomes are difficult to disentangle from those of RT [5].

The presented ESCaRa-Study (Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients) focused on cardiac mortality and cardiac morbidity in breast cancer patients in Germany treated between 1998 and 2008 with contemporary RT. ESCaRa continues the PASSOS-Heart Study [15, 16] with additional 5.5 years of systematic mortality follow-up and a second questionnaire survey on cardiac morbidity in 2019.

Methods

Study design and study population

The ESCaRa-study is a retrospective multicenter cohort study. Eligible breast cancer patients were diagnosed and treated between 01/1998 and 12/2008 at Mainz University Medical Center, at the Ulm University Hospital or at one of 16 partner clinics in the vicinity of Ulm. Inclusion criteria were a histologically confirmed primary and loco-regional breast cancer disease, either an invasive carcinoma or a carcinoma in situ (CIS). Since the focus was on breast cancer patients with a good prognosis, women with primary metastatic disease or bilateral breast cancer were not included.

Individual data on breast cancer disease, therapy and co-morbidities were abstracted from the patients' hospital records: date of diagnosis, age at diagnosis, date of birth, laterality, TNM-stage, histological subtype, grading, lymphatic and vascular invasion, and hormonal parameters. Treatment information included type of surgery, adjuvant systemic chemotherapy, adjuvant endocrine therapy, and detailed information on administered adjuvant RT. Data on first recurrences as well as on second primary tumors were obtained. Furthermore, the history of malignant diseases prior to breast cancer was abstracted.

Cardiac morbidities diagnosed at the time of breast cancer treatment were recorded, if available from the pre-anesthetic interview documentation: New York Heart Association (NYHA) cardiac score at the time of surgery, history of myocardial infarction, coronary heart disease, angina pectoris, dysrhythmia, vitium cordis, stroke, and pacemaker.

Mortality follow-up and mortality endpoints

The individual follow-up was carried out by contacting the corresponding compulsory population registry of the municipality of the last known residence in order to assess the vital status on June 30, 2018. Death certificates were obtained from the local health authority of the place of death. The underlying causes of death were coded according to the 10th revision of the International Classification of Diseases (ICD).

The definition of mortality endpoints was adapted from [17]. The primary mortality endpoint is defined as all deaths certified as heart disease (cardiac infarction I21–I23; chronic ischemic heart disease I25.0–I25.9; acute ischemic heart disease I21.0–I24.9; congestive heart failure I50.0–I50.9; angina pectoris I20.0–I20.9; cardiac arrest I46; dysrhythmias, conduction disorder I44.0–I49.9; vitium cordis I34.0–I37.9). Additional analyses were carried out for all-cause mortality (A00-Y98).

Questionnaire survey and morbidity endpoints

In 2014, a questionnaire was mailed to former patients who were reported alive. It contained 25 questions on sociodemographic variables, clinical diagnoses of cardiac illness before or after cancer treatment, potential risk factors for cardiac disease, the duration of hormonal therapy, and about cancer recurrence. Patients who did not wish to complete the extensive questionnaire could fill out a short form with questions on cardiac illness and on cardiovascular risk factors (supplementary information: SI 1). In 2019, a second questionnaire survey was conducted: the short form was sent out to patients who (1) participated in the first survey, (2) who were reported to be alive and (3) who gave permission for a second contact.

An incident cardiac event was defined to be present if a participant reported any of the following individual events after breast cancer therapy: Myocardial infarction, angina pectoris, congestive heart failure, arrhythmia, or valvular heart disease [17].

RT techniques

The patients underwent RT at the University Medical Centers in Mainz, Ulm or at one of 16 collaborative partner clinics, who had their own RT unit. The whole breast was treated by three-dimensional conformal RT using two tangential fields of 6 MV photons. The total radiation dose to the planning target volume typically was 50 Gy, administered in 25 fractions with 5 fractions per week. For breast conserving treatment, an additional boost dose of 10 Gy was usually delivered to the tumor bed. Optionally, RT could include a supraclavicular field as well as an anterior–posterior parasternal field to cover the internal mammary lymph nodes [18, 19]. Active breathing modalities or altered fractionation were not applied in this cohort.

Statistical methods

Individual follow-up (time at risk) started with the date of diagnosis of primary breast cancer. We included all diagnoses occurring since January 1, 1998. The end of the mortality follow-up was defined as the date of death, last information date, or June 30, 2018, whichever occurred first. The questionnaire-based assessment of morbidity included all self-reported diagnoses occurring since January 1, 1998. For patients who responded to the questionnaire, the end of follow-up was defined as the event date (reported year of cardiac diagnosis), last information date, or June 30, 2018, whichever occurred first.

Missing information on chemotherapy, endocrine therapy and body mass index (BMI) at diagnosis was imputed via multiple imputation using fully conditional specification method, assuming data missing at random. We used SAS procedures PROC MI and PROC MIANALYZE to create 20 imputed datasets, and pooled individual modeling results based on the imputed datasets using Rubin's Rule. Complete case analyses were conducted as sensitivity analysis [20–23].

For patients who received RT, the Kaplan–Meier Method was used to assess survival. Survival of patients with left- vs. right-sided RT was compared by the Mantel–Haenszel (log-rank) test [24]. Multivariable Cox-Regression was used to assess the association of cardiac events with breast cancer laterality as a surrogate measure for the level of radiation exposure [25]. Hazard ratios (HR) and corresponding 95%-confidence intervals (CI) were estimated. The significance level was set at 5% without correction for multiple testing. The analysis was adjusted for potential confounders selected a-priori based on theoretical considerations (age at breast cancer diagnosis, year of breast cancer diagnosis, baseline cardiac morbidity (yes/no), application of chemotherapy (yes/no), application of endocrine therapy (yes/no), and BMI). To allow for a potentially non-monotonic association of BMI with cardiac endpoints, BMI was included as a cubic spline with four internal knots. The analysis was restricted to patients with at least 1 year of follow-up, and only cardiac deaths that occurred at least 1 year after breast cancer diagnosis. Incident cardiac events were only considered if the reported calendar year was later than the year of breast cancer diagnosis. If women participated in both surveys, the first morbidity event was considered for the analysis. The proportional hazards assumption was checked by examining complementary log–log plots for categorical variables, and by assessing the correlation of scaled Schoenfeld residuals with log survival time for continuous variables. For a sensitivity analysis, data were censored at time of diagnosis of a recurrent event since additional RT or chemotherapy may have occurred thereafter.

SAS for windows, version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

Results

Description of the cohort at baseline

A total of 11,982 women met the inclusion criteria. Most patients were diagnosed after 2000 (Table 1). The mean age at diagnosis was 60.9 years (range 18–101 years). A total of 2925 (24.4%) patients received no RT. These women were older on average (mean age 66.7 years) compared to patients who were treated with RT (mean age 59.0 years). Patients who did not receive RT had a higher percentage of CIS compared to irradiated patients. This is consistent with 67.4% of women in this group having had mastectomy without adjuvant chemotherapy and a higher frequency of

Table 1 Characteristics of the study population by radiotherapy group

	No radiation therapy	Yes radiation therapy	
		Right-sided	Left-sided
Year of diagnosis			
1998–2000	210 (7.2%)	321 (7.2%)	334 (7.2%)
2001–2003	604 (20.6%)	710 (16.0%)	786 (17.0%)
2004–2006	1272 (43.5%)	1864 (42.1%)	1912 (41.4%)
2007–2008	839 (28.7%)	1539 (34.7%)	1591 (34.4%)
Age at diagnosis (years)			
Mean	66.7	58.7	59.3
SD*	15.5	12.3	12.0
T-stage (*N*, %)			
1	955 (32.6%)	2458 (55.4%)	2568 (55.6%)
2	986 (33.7%)	1427 (32.2%)	1454 (31.4%)
3	114 (3.9%)	151 (3.4%)	191 (4.1%)
4	188 (6.5%)	167 (3.8%)	174 (3.8%)
In situ	548 (18.7%)	176 (3.9%)	198 (4.3%)
Unknown	133 (4.6%)	55 (1.2%)	38 (0.8%)
N-stage (*N*, %)			
0	1477 (50.5%)	2633 (59.4%)	2,738 (59.2%)
1	585 (20.0%)	1065 (24.0%)	1,094 (23.7%)
2	153 (5.2%)	380 (8.6%)	378 (8.2%)
3	76 (2.6%)	228 (5.1%)	244 (5.3%)
X	634 (21.7%)	128 (2.9%)	169 (3.6%)
Chemotherapy (*N*, %)			
Yes	606 (20.7%)	2,254 (50.8%)	2,266 (49.0%)
No	2309 (78.9%)	2140 (48.3%)	2323 (50.3%)
Unknown	10 (0.4%)	40 (0.9%)	34 (0.7%)
Endocrine therapy (*N*, %)			
Yes	1604 (54.8%)	3273 (73.8%)	3411 (73.8%)
No	1243 (42.5%)	1012 (22.8%)	1070 (23.1%)
Unknown	78 (2.7%)	149 (3.4%)	142 (3.1%)
Type of surgery			
None	82 (2.8%)	16 (0.4%)	14 (0.3%)
Breast conserving	851 (29.1%)	3706 (83.6%)	3837 (83.0%)
Mastectomy	1971 (67.4%)	710 (16.0%)	772 (16.7%)
Unknown	21 (0.7%)	2 (0.05%)	0 (0.0%)
History of cardiac disease[a] (*N*, %)			
Yes	355 (12.1%)	383 (8.6%)	371 (8.0%)
No information	2570 (87.9%)	4051 (91.4%)	4252 (92.0%)
BMI[b] at diagnosis			
< 18.5	65 (2.2%)	69 (1.6%)	58 (1.3%)
18.5–24.9	1187 (40.6%)	1810 (40.8%)	1877 (40.6%)
25.0–29.9	801 (27.4%)	1364 (30.8%)	1426 (30.8%)
≥ 30.0	454 (15.5%)	816 (18.4%)	869 (18.8%)
No information	418 (14.3%)	375 (8.5%)	393 (8.5%)
Total *N* = 11,982	2925 (100%)	4434 (100%)	4623 (100%)

*SD standard deviation

[a]History of cardiac disease at the time of breast cancer diagnosis: cardiac infarction or coronary heart disease or angina pectoris or NYHA ≥ 3 or dysrhythmia or vitium cordis or pacemaker

[b]*BMI* body mass index

previous cardiac disease compared to irradiated women. More than 75% of the patients ($n = 9.057$) received RT as part of the primary treatment. Proportions of women with left-sided or right-sided breast cancer among those with RT were similar. The distribution of age at diagnosis, calendar year of diagnosis, staging, the application of chemotherapy, endocrine therapy and the type of surgery were similar for left- and right-sided tumors. A history of cardiac disease was confirmed in approximately 8% in both laterality groups.

In a randomly selected sample of 769 irradiated breast cancer patients, electronic treatment planning records were obtained. The average mean heart dose (median) was 4.6 Gy (3.7 Gy) for left-sided RT, and 1.7 Gy (1.4 Gy) for right-sided RT [18].

Mortality follow-up

Vital status of the cohort was observed until June 30, 2018 yielding a median follow-up period of 11.1 years. At the end of the follow-up period, more than 65% of the former breast cancer patients were still alive (Table 2). Among those women who did not receive RT, the proportion of deaths was 51.8% compared to 27.9% in women with RT. For $n = 126$ (3%) of deceased cohort members, no cause of death could be ascertained.

The median survival time among women with RT was 11.4 years (Fig. 1). The overall survival was equivalent between left- and right-sided irradiation at 5-, 10-, and 15-year follow-up increments. The 20-year overall survival was 59% (95%CI 55.2–62.8) in right-sided and 55% (95%CI 48.2–60.8) in left-sided tumors. This result was based on 56 cases only.

Association between radiotherapy and mortality

Figure 2 shows the association of laterality with cardiac mortality when controlling for confounders and effect-modifiers. In RT-patients, there was no evidence for an effect of laterality. The HR of cardiac mortality for left-sided vs. right-sided RT was 1.09 (95%CI 0.85–1.41). A history of cardiac disease and higher age at diagnosis were associated with significantly increased cardiac mortality, while chemotherapy was not a significant risk factor. After stratification for the length of follow-up, a statistically not

Table 2 Overall survival of the ESCaRa-cohort (end of observation June 30, 2018)

	Radiotherapy no (*n*, %)	Radiotherapy yes (*n*, %)	All (*N*)
Alive	1382 (47.3%)	6435 (71.1%)	7817 (65.2%)
Dead	1514 (51.7%)	2523 (27.9%)	4037 (33.7%)
Lost to follow-up	29 (1.0%)	99 (1.0%)	128 (1.1%)
Total	2925 (100%)	9057 (100%)	11,982 (100%)

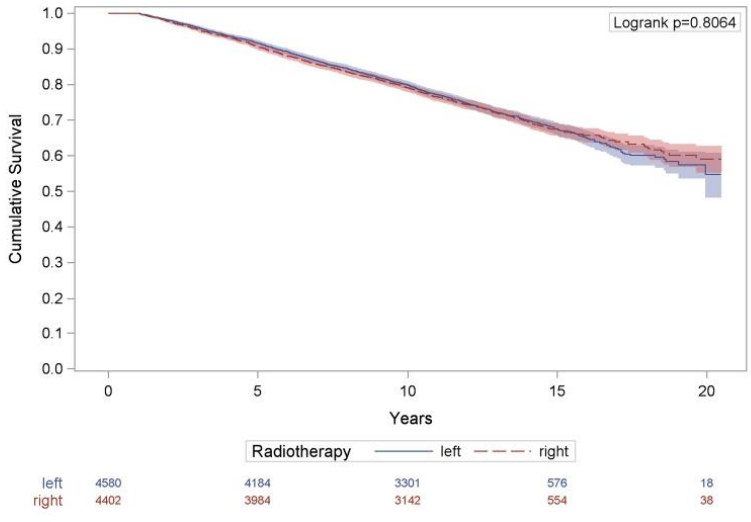


Fig. 1 Overall survival of patients with radiotherapy compared by tumor laterality. Shaded areas: 95% confidence intervals

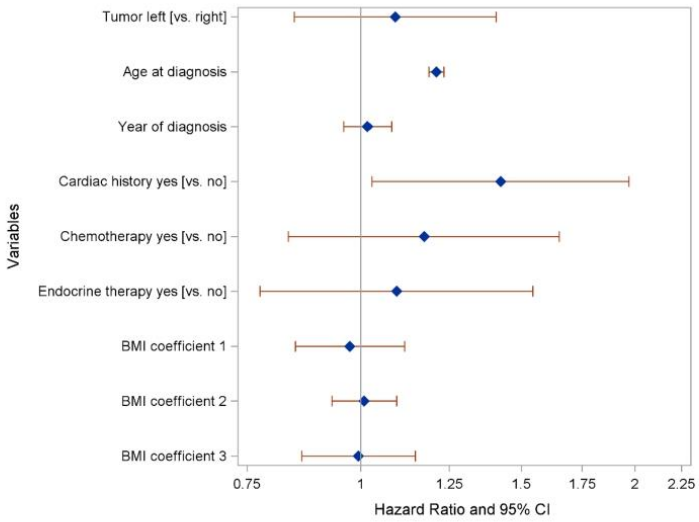


Fig. 2 Multivariate cox regression: hazard ratios with 95% confidence intervals for cardiac mortality risk in breast cancer patients with radiotherapy. *BMI* body mass index: adjustments by using restricted cubic splines with four internal knots, *CI* confidence interval

BMI, Body Mass Index: adjustments by using restricted cubic splines with 4 internal knots; CI, Confidence Interval

significant increased risk for cardiac mortality due to laterality was detected for an observational period of more than 10 years (HR = 1.35 [95%CI 0.88–2.06]) (Table 3). Sensitivity analyses with censoring at the time of a recurrent event and a complete case analysis did not reveal any different results (SI 2, SI 3). For overall mortality (SI 4), there was no evidence for an effect of laterality in patients treated with RT (HR = 0.97; 95%CI 0.90–1.05). However, in contrast to cardiac mortality, chemotherapy was a significant risk factor for overall mortality (HR = 1.51, 95%CI 1.39–1.65).

Table 3 Multivariate cox regression: cardiac mortality risk in breast cancer patients with radiotherapy and stratification for duration of follow-up

	All[a]		Duration of follow-up			
			≥ 1–≤ 10 years[b]		> 10 years[c]	
	HR	95%CI	HR	95%CI	HR	95%CI
RT, left vs. right	1.09	(0.85–1.41)	0.99	(0.72–1.36)	1.35	(0.88–2.06)
Age at diagnosis	1.21	(1.19–1.23)*	1.15	(1.12–1.18)*	1.21	(1.17–1.26)*
Year of diagnosis	1.02	(0.96–1.08)	0.86	(0.81–0.91)*	1.13	(1.00–1.28)
Cardiac history (yes/no)	1.42	(1.03–1.97)*	0.99	(0.64–1.54)	1.91	(1.16–3.15)*
Chemotherapy (yes/no)	1.17	(0.83–1.65)	0.86	(0.53–1.39)	1.60	(0.97–2.66)
Endocrine therapy (yes/no)	1.09	(0.77–1.54)	0.92	(0.61–1.38)	1.71	(0.90–3.26)
BMI coefficient 1**	0.97	(0.85–1.12)	0.95	(0.81–1.11)	1.02	(0.81–1.30)
BMI coefficient 2	1.01	(0.93–1.09)	1.02	(0.94–1.11)	0.95	(0.82–1.10)
BMI coefficient 3	1.00	(0.86–1.15)	0.97	(0.84–1.13)	1.11	(0.86–1.43)

BMI body mass index, 95%CI 95% confidence interval, *HR* hazard ratio, *RT* radiotherapy

*Statistically significant

**BMI coefficient: adjustments for BMI by using restricted cubic splines with four internal knots

[a] Analysis based on 8982 patients: total cohort ($N = 11{,}982$) with at least 1-year follow-up (11,719), with radio therapy (8982); $n = 240$ cases of cardiac mortality

[b] Analysis based on N 2539 individuals with 152 cases of cardiac mortality

[c] Analysis based on N 6443 and 88 cases of cardiac mortality

Morbidity follow-up

In 2014 a total of 5388 questionnaires were received (median follow-up period 8.3 years). The second questionnaire survey had a total of 1.831 responders with a median follow-up of 12.5 years.

Among responders who were treated with RT, at least one incident cardiac event after breast cancer therapy was reported by 497 individuals (from both surveys). Arrhythmia was the most frequent event with an almost equal distribution according to laterality with 12.6% of women with a left-sided tumor (yes 288, no 2,005) and 12.0% of those with a right-sided tumor (yes 261, no 1,920). Myocardial infarction was reported by 2.5% of women (yes 58, no 2,235) with a left-sided tumor and by 1.7% (yes 38, no 2,143) of those with a right-sided tumor.

Association between radiotherapy and cardiac morbidity

Tumor laterality as a surrogate for radiation exposure was not identified as a significant risk factor for any type of cardiac event (Fig. 3). The hazard ratio for left-sided vs. right-sided tumors was 1.05 (95%CI 0.88–1.25). Significant risk factors for cardiac morbidity included a history of cardiac disease at baseline and chemotherapy. Age at diagnosis of breast cancer is a significant risk factor for cardiac morbidity (HR = 1.02; 95%CI 1.01–1.03). Sensitivity analysis did not reveal a significantly higher risk for left-sided RT compared to right-sided RT after more than 10 years of follow-up (Table 4).

Discussion

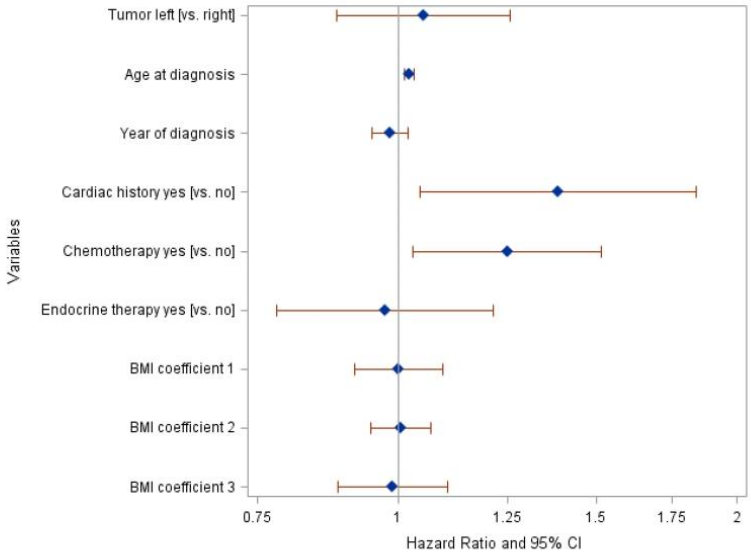
The ESCaRa-Study investigated the relationship between 3D-conformal RT and long-term cardiac mortality and morbidity risk in a cohort of 11,982 patients treated between 1998 and 2008 in Germany. We evaluated the impact of left-sided vs. right-sided radiation as a proxy measure for the exposure of the heart to ionizing radiation.

Main results

A multivariate analysis revealed no evidence for an effect of laterality on cardiac mortality in 9057 women treated with RT (HR, left-sided vs. right-sided tumor 1.09; 95%CI 0.85–1.41) after a median follow-up time of 11.1 years. Tumor laterality was not identified as a significant risk factor for incident cardiac morbidity (HR = 1.05; 95%CI 0.88–1.25).

Comparison to earlier studies

A Surveillance, Epidemiology and End Results Study (SEER) evaluated the difference in cardiac mortality among



BMI, Body Mass Index: adjustments by using restricted cubic splines with 4 internal knots;

CI, Confidence Interval

Fig. 3 Multivariate cox regression: hazard ratios with 95% confidence intervals for cardiac morbidity in breast cancer patients with radiotherapy. *BMI* body mass index: adjustments by using restricted cubic splines with four internal knots, *CI* confidence interval

Table 4 Multivariate cox regression: cardiac morbidity risk in breast cancer patients with radiotherapy and stratification for duration of follow-up

	All[a]		Duration of follow-up			
			≥ 1- ≤ 10 years[b]		> 10 years[c]	
	HR	95%CI	HR	95%CI	HR	95%CI
RT, left vs. right	1.05	(0.88–1.25)	0.94	(0.77–1.15)	1.09	(0.73–1.63)
Age at diagnosis	1.02	(1.01–1.03)*	1.01	(1.00–1.02)*	1.02	(1.00–1.04)*
Year of diagnosis	0.99	(0.95–1.02)	0.77	(0.75–0.80)*	0.88	(0.80–0.97)*
Cardiac history (yes/no)	1.39	(1.05–1.84)*	1.19	(0.87–1.64)	0.96	(0.49–1.90)
Chemotherapy (yes/no)	1.25	(1.03–1.52)*	1.14	(0.92–1.41)	1.20	(0.77–1.86)
Endocrine therapy (yes/no)	0.97	(0.78–1.21)	0.82	(0.64–1.06)	0.98	(0.59–1.60)
BMI coefficient 1**	1.00	(0.92–1.09)	0.98	(0.89–1.08)	1.06	(0.86–1.31)
BMI coefficient 2	1.01	(0.95–1.07)	1.00	(0.95–1.06)	1.00	(0.86–1.16)
BMI coefficient 3	0.99	(0.88–1.11)	1.00	(0.90–1.10)	0.99	(0.75–1.30)

BMI body mass index, 95%CI 95% confidence interval, *HR* hazard ratio, *RT* radiotherapy

*Statistically significant

**BMI coefficient: adjustments for BMI by using restricted cubic splines with four internal knots

[a]Analysis based on 4379 patients: total sub-cohort (5388) with at least 1-year follow-up (5280), who received radio therapy (4379); $n = 497$ cases of incident cardiac morbidity

[b]Analysis based on N 883 individuals with 402 cases of cardiac morbidity

[c]Analysis based on N 3496 and 95 cases of cardiac morbidity

breast cancer patients who received RT. For women irradiated with contemporary techniques and in more recent years (1993 +), there was little evidence for an increased cardiac mortality considering laterality as a proxy for the radiation exposure of the heart [26, 27]. This finding was supported by Li et al. [28] who analyzed SEER-data of more than 168,000 breast cancer patients diagnosed between 2000 and 2008. After a median follow-up time of 8.8 years, no association between tumor laterality and cardiac-related mortality was found. Investigations of smaller cohorts agree with these observations [29–31], suggesting that newer RT techniques may not increase the cardiac mortality risk. A large cohort study with a total of 1,934,248 breast cancer patients from 22 countries evaluated the difference in cardiac mortality among left and right breast irradiated women [9]. Considering all women diagnosed 1990–2002 the cardiac mortality rate ratio left vs. right was not significantly different from unity (Relative Risk = 0.98; 95%CI 0.93–1.02). The mean length of follow-up was 6.7 years which might explain the lack of evidence [9]. Overall, our results on cardiac mortality and modern RT in German breast cancer patients are consistent with the results of earlier studies. However, even a median follow-up period of 11.1 years might not to be sufficient to detect a possible excess mortality.

Studies on tumor laterality as a potential risk factor for cardiac morbidity in patients treated after 1990 show inconclusive results. Studies in older women aged 65 + found no significant increase in heart disease [30, 32, 33]. Registry-based studies included the full age range of breast cancer patients [34–36] and indicated a moderately increased risk, based on large sample sizes. Among Danish patients irradiated with modern RT (2008–2016), the incidence rate ratio for cardiac event (left vs. right-sided) was 0.90 (95%CI 0.69–1.16) after a median follow-up of 6.9 years [37]. The ESCaRa-Study failed to demonstrate an increased risk of cardiac morbidity following left breast RT in German patients, even after a follow-up period of 12 years.

Confounding and interaction

Rehammar et al. [36] have shown that anthracycline-based chemotherapy further raises the risk of heart disease in left-sided compared to right-sided irradiation. In the ESCaRa-cohort only 50% of the irradiated patients received adjuvant chemotherapy. We found a risk increase for cardiac outcomes related to chemotherapy, but without statistical significance for cardiac mortality. However, chemotherapy was a statistically significant risk factor for all-cause mortality (HR = 1.51; 95%CI 1.39–1.65). This observation might be related to confounding by indication and competing risks: a severe breast cancer disease associated with a poorer prognosis indicates the application of chemotherapy. An unfavorable cancer staging and worse survival might remove a subject from being at risk for long-term cardiovascular disease or cardiovascular death.

Obesity is one of the most frequently reported risk factor for cardiovascular disease [38] and an established risk factor for postmenopausal breast cancer [39].The presented cohort did not identify BMI as significant cardiac risk factors. While BMI was not a statistically significant risk factor for cardiac mortality in multivariate analysis, BMI < 20

and > 23 were descriptively associated with higher risk which flattened at BMI > 28 (SI 5).

Strengths and limitations

The ESCaRa-Study permitted an effective mortality follow-up (loss to follow-up 1.1%) and a comprehensive ascertainment of cause of death (completeness 97%). The available information on morbidity endpoints in the present study comes from a questionnaire survey with a moderate to high response rate (58.9% first survey 2014; 80% follow-up survey 2019). Further strengths of the present study include the extensive clinical documentation of breast cancer patients treated in certified breast centers. By including a comparably large number of observed cardiac events (240 cases of cardiac mortality; 497 cases of cardiac morbidity), the statistical model could adjust for several cardiac risk factors that are potential modifiers for the effect of tumor laterality on risk for late cardiac events.

The median mortality follow-up time in the ESCaRa-Study was 11.1 years, the median follow-up period for morbidity endpoints was 12.4 years. No statistically significant evidence for an increased risk of cardiac mortality or cardiac morbidity in irradiated women was found. It is possible that the follow-up period was too short to detect long-term adverse health hazards of RT. The risk for coronary heart disease started within the first decade, whereas the risk for cardiac death started from the second decade after RT [7].

When deriving inferences from questionnaire survey data, it is important to consider any self-selection bias. The second survey (2019) focused on responders of the first survey, who gave permission for being contacted again. This diminished the targeted sample and may have introduced selection of healthy survivors. Survey participants, especially those who participated in both surveys, may have been motivated by a higher interest in late cardiac effects which might be associated with a healthier life-style compared to non-responders. Furthermore, self-reported events may be prone to information bias due to restrictions in memory, a lack of fully understanding medical diagnoses, or selective reporting [40]. However, a validation study revealed moderate to fair agreement between self-reported events compared with medical records from general practitioners [41].

Finally, laterality is a crude proxy measure for the exposure of radiation to the heart. In terms of an increased risk of heart disease many years after irradiation, scientific efforts are needed to investigate susceptible regions and structures of the heart, to assess exact cardiac doses, and to ascertain a possible threshold and dose–response relationship. In the future, it is essential to individualize treatment according to tumor characteristics, treatment modalities (endocrine and immunotherapy) and patients characteristics [42, 43].

Conclusions

The population-based ESCaRa-study offers continued support for the efficacy of modern breast cancer treatment. We found no indication that radiotherapy for left-sided breast cancer in German patients is a strong limiting factor for survival in the first decade after breast cancer therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06412-3.

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Data availability Raw data compliant with the institutional confidentiality policies can be available upon request from the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The ESCaRa-Study has been approved by the Ethics Committee of Rhineland-Palatinate, Mainz and the Ethics Committee of the University of Ulm. The data protection officer approved using the patients' hospital records and the performing of a mortality follow-up for the entire cohort without written informed consent of the patients. For the questionnaire survey, individual informed consent was obtained.

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4 Article II: A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany

4.1 Preliminaries Article II

As described (Section 1.3.2), studies using individual dose estimates to assess the risk for cardiac late effects in female breast cancer patients are sparse and mainly include radiotherapy treatment before 2000 where conventional 2D radiotherapy was still present[76 82 122 123], and for Germany so far non-existent. With Article II of the cumulative PhD-thesis this research gap for Germany is targeted.

The nested case-control study, presented in Article II, includes 494 cases and 988 matched controls treated with 3D-conformal radiotherapy for breast cancer in Germany in 1998-2008, making it the second largest study published on this topic. Over 75% of the cases and controls were treated after 2000, which is in combination with the size of the study up to this point unique internationally. In Article II dose-response analyses for the complete heart and the LAHW including the LAD are presented. For both, the complete heart and the LAHW analyses for DMEAN and V5Gy were carried out. Heart dosimetry was done for a sample of patients from the same cohort the case-control study is nested in (ESCaRa-Study) (Section 2.4). Contouring of the heart and the LAHW including the LAD was performed according to a heart atlas developed for retrospective epidemiological studies [125], with good inter-observer contouring agreement with respect to structure geometry and dose to the LAHW. Based on cumulative dose-volume histograms for each patient and heart structure the DMEAN and V5Gy was calculated [78]. For 91 cases and 182 controls of the 494 cases and 988 controls individual estimates for DMEAN and V5Gy values for the complete heart and the LAHW could be extracted from the dosimetry sample. For the remaining 403 cases and 806 controls that were not part of the dosimetry sample doses were imputed based on a validated prediction model [105]

4.2 Article II

Baaken D, Merzenich H, Schmidt M, Bekes I, Schwentner L, Janni W, Wöckel A, Meyer M, Mose S, Merz T, Ghilescu V, Renner J, Bartkowiak D, Wiegel T, Blettner M, Schmidberger H, Wollschläger D. (2022). A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany. *The Breast* 65: 1-7. https://doi.org/10.1016/j.breast.2022.05.007

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A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany

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ABSTRACT

Background: Previous studies with the majority of breast cancer (BC) patients treated up to 2000 provided evidence that radiation dose to the heart from radiotherapy (RT) was linearly associated with increasing risk for long-term cardiac disease. RT techniques changed substantially over time. This study aimed to investigate the dose-dependent cardiac risk in German BC patients treated with more contemporary RT.

Methods: In a cohort of 11,982 BC patients diagnosed in 1998–2008, we identified 494 women treated with 3D-conformal RT who subsequently developed a cardiac event. Within a nested case-control approach, these cases were matched to 988 controls. Controls were patients without a cardiac event after RT until the index date of the corresponding case. Separate multivariable conditional logistic regression models were used to assess the association of radiation to the complete heart and to the left anterior heart wall (LAHW) with cardiac events.

Results: Mean dose to the heart for cases with left-sided BC was 4.27 Gy and 1.64 Gy for cases with right-sided BC. For controls, corresponding values were 4.31 Gy and 1.66 Gy, respectively. The odds ratio (OR) per 1 Gy increase in dose to the complete heart was 0.99 (95% confidence interval (CI): 0.94–1.05, $P = .72$). The OR per 1 Gy increase in LAHW dose was 1.00 (95% CI: 0.98–1.01, $P = .68$).

Conclusions: Contrary to previous studies, our study provided no evidence that radiation dose to the heart from 3D-conformal RT for BC patients treated between 1998 and 2008 was associated with risk of cardiac events.

1. Introduction

A cornerstone in breast cancer (BC) therapy, radiotherapy (RT) reduces local recurrence and BC-related mortality [1,2]. However, RT-induced risk for cardiac events is of clinical relevance to a growing number of long-term survivors [3]. Advances in RT, including improved treatment planning based on 3D-CT imaging [4], have reduced cardiac radiation dose [5]. Nevertheless, the heart remains exposed to ionizing radiation mainly depending on tumor laterality and individual anatomic risk factors [6]. On average, RT for left-sided BC is associated with higher radiation dose to the heart compared to right-sided BC [7]. Some studies have indicated an increased risk for radiation-induced cardiac effects based on tumor laterality [8,9], while others have not [10,11]. However, using laterality as a surrogate measure of exposure ignores

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large within-group heterogeneity of radiation doses in left-sided irradiated patients due to differences in individual anatomy and in radiation field geometry [7]. Therefore, dose-response analyses based on individual cardiac radiation dose estimates are better suited to quantify the radiation-induced cardiac risk. Darby et al. [12] showed a linear dose-response relationship between the mean dose to the whole heart (MHD) and risk of major coronary events in BC patients who received RT between 1958 and 2001 [12]. Of all included patients 76.3% were treated up to 1990, clearly before modern treatment planning came into widespread use. Furthermore, a systematic review and pooled analysis of 75 clinical trials with 40.781 patients mainly treated before 1990 and random assignment to RT of breast cancer patients identified an increased risk for cardiac mortality (rate ratio 1.30, 95% confidence interval (CI) 1.15–1.46) [13].

Using MHD to characterize cardiac radiation exposure has limitations since the heart is not a homogeneous organ. Damage to certain functional substructures, such as the coronary arteries, might be associated with characteristic late effects like ischemic heart disease [14]. Current studies raise the question whether dose to the left anterior descending (LAD) coronary artery is a better predictor for cardiac late effects compared to the MHD [15] because of the major role of the LAD in myocardial perfusion [14]. Furthermore, the heterogeneity of the cardiac dose distribution should be taken into account. Small regions of the heart in patients with left-tangential RT receive doses of ≥20 Gy even when MHD is low [5]. Using alternative dose metrics for risk assessment is also currently being investigated [16]. In a recent study [17], the volume of the left ventricle receiving ≥5 Gy (V5Gy) was shown to be a better predictor than MHD for acute coronary events in patients with BC. Jacobse and colleagues [18] identified an association between V5Gy for the complete heart and the rate of myocardial infarction. However, their results did not indicate that V5Gy was a better predictor compared to MHD.

Data about the risk of cardiac late effects in BC patients with contemporary RT based on individual heart dosimetry is still sparse. Here, we present the results of a nested case-control study to investigate a potential dose-response relationship between cardiac radiation exposure and cardiac late events in women diagnosed with BC between 1998 and 2008 in Germany, of whom >75% were treated after 2000.

2. Material and methods

2.1. Cohort population

The case-control study is nested within the ESCaRa cohort study (Epidemiological Study on Cardiac late effects and second malignancies after Radiotherapy in breast cancer patients) of 11,982 female BC patients [19]. Among them, 9057 (75.6%) were treated with 3D-conformal RT between 1998 and 2008 at Mainz University Medical Center's Department of Obstetrics and Gynaecology, Ulm University Hospital's Department of Gynaecology and Obestrics, or at one of 16 certified breast centers in the vicinity of Ulm. We included patients with histologically confirmed primary and locoregional BC, either an invasive carcinoma or a carcinoma in situ. We excluded patients with primary metastatic disease or bilateral BC. Details of the cohort were published previously [10,11]. In short, individual clinical data on disease characteristics, therapy, and comorbidities were obtained from patients' hospital records. These included date of birth and date of diagnosis, tumor laterality, TNM-stage, histological subtypes, grading, lymphatic and vascular invasion, hormonal status (estrogen and progesterone receptor), and treatment details.

An individual mortality follow-up was carried out to ascertain the vital status as of December 2012 via the compulsory municipal population registries of the patients' last known residences. The underlying cause of death was coded according to the 10th revision of the International Classification of Disease (ICD), based on death certificates from local health authorities. Data on cardiac morbidity were assessed via a self-administered questionnaire in 2014 [11].

2.2. Nested case-control study

Cases and controls were selected among patients of the cohort who received 3D-conformal RT and had at least one year of follow-up. We applied 1:2 incidence-density sampling of controls with replacement [20]. Cases were defined as patients with RT who experienced a cardiac event later than the calendar year of their BC diagnosis. We distinguished two types of cardiac events: Either a self-reported incident event of cardiac morbidity from the questionnaire in 2014, or cardiac mortality until December 31st, 2012. Cardiac morbidity included myocardial infarction, angina pectoris, congestive heart failure, dysrhythmias or valvular heart disease. Cardiac mortality was defined as the following causes of death: cardiac infarction (ICD I21–I23), chronic ischemic heart disease (ICD I25.0–25.9), acute ischemic heart disease (ICD I21.0–I24.9), congestive heart failure (ICD I50.0–I50.9), angina pectoris (ICD I20.0–I20.9), cardiac arrest (ICD I46), dysrhythmias and conduction disorder (ICD I44.0–I49.9), and vitium cordis (ICD I34.0–I37.9) [21].

Irradiated patients were eligible as controls if they had not experienced the type of cardiac event as the index case (cardiac morbidity or cardiac mortality) at the corresponding follow-up time of the event of the index case. Controls were matched based on their age at BC diagnosis (5-year age categories), year of BC diagnosis (5-year categories), the study center (Mainz, Ulm, partner clinic), and presence of a cardiac comorbidity at the time of the BC diagnosis. These baseline cardiac comorbidities were defined as having a New York Heart Association (NYHA) cardiac score ≥3 or a history of myocardial infarction, coronary heart disease, angina pectoris, dysrhythmias, vitium cordis, a stroke or pacemaker use. Information on baseline cardiac comorbidities was derived from clinical records, in particular from preoperative evaluation and preparation for anesthesia. When a relevant comorbidity was not mentioned in the documentation, it was coded as "No/unknown". This label reflects that absence of a documented comorbidity might have resulted from a physician actively requesting the information that no comorbidity was present, or from failure of the physician to request that information.

2.3. Dosimetry

Independently from the nested case-control study, we selected a sample of 1353 patients from the ESCaRa cohort representative in terms of age and tumor laterality in order to retrospectively estimate individual heart dosimetry. Dosimetry details are described elsewhere [7]. Using 3D-conformal RT with tangential fields of 6 MV photons, the total radiation dose with regard to the planning target volume was typically 50 Gy. For breast-conserving treatment, an additional boost dose of 10 Gy was usually delivered to the tumor bed. RT could also include lymph node fields. In addition to the complete heart, several geometric surrogate volumes to functional anatomical heart structures were individually contoured, including the left anterior heart wall (LAHW). The LAHW contains the LAD, an important organ at risk that can be exposed to much higher doses compared to the complete heart [22–24]. The contouring was performed according to a heart atlas developed for retrospective epidemiological studies [25]. The volume-weighted mean dose (DMEAN) and the percentage volume of the structure receiving ≥5 Gy (V5Gy) were calculated for the complete heart and for the LAHW based on exported dose-volume histograms. The final sample of the nested case-control study consisted of 494 cases and 988 controls. For 91 cases and 182 corresponding controls, we were able to extract individually estimated DMEAN and V5Gy values for the complete heart and for the LAHW from the dosimetry sample. For 403 cases and 806 controls without individual dosimetry, doses were imputed as described below [22].

2.4. Statistical analysis

We used conditional multivariable logistic regression to calculate odds ratios (OR) and corresponding 95% Wald CI for estimated coefficients, conditioning on strata defined by the matching groups. The significance level was set at 5% without correction for multiple testing. We selected chemotherapy (yes/no), endocrine therapy (yes/no), and body mass index (BMI) (≥25.0/<25.0) as covariates based on a-priori theoretical considerations.

Multiple imputation using fully conditional specification methods [26,27] was used to deal with missing information on DMEAN and V5Gy for the complete heart and the LAHW, assuming data was missing at random. Doses were imputed using a previously validated dose prediction model based on age at breast cancer diagnosis, year of breast cancer diagnosis, study center, laterality and BMI [22]. We also used multiple imputation of missing values for BMI, chemotherapy, and endocrine therapy.

We evaluated potential nonlinearity of the dose-response association by adding a linear-quadratic term to our dose-response model for DMEAN of the complete heart. Goodness of fit was assessed by Akaike information criterion (AIC). In sensitivity analyses, we investigated a different dose metric (V5Gy) and a different functional substructure (LAHW). Furthermore, we carried out dose-response analyses for dose categories using quintiles from the observed distribution for DMEAN. For V5Gy, we used <10% as the reference category, and 10%–29% and ≥30% as further categories to ensure comparability with a previous study [18]. We also conducted sensitivity analyses restricted to only cases and their corresponding controls with available dose information from the dosimetry sample.

SAS 9.4 (SAS Institute North Carolina) was used for all analyses.

3. Results

3.1. Patient characteristics

Characteristics of the 494 cases and 988 controls included in the analysis are described in Table 1. The mean age at BC diagnosis was 63.14 for cases and 63.10 for controls. Most cases and controls were diagnosed with BC in 2004–2006 (43.12% and 44.64%, respectively). The cancer stage, individual risk factors at time of diagnosis (BMI, history of cardiac disease) and therapy-related characteristics were equally distributed between cases and controls (Table 1).

3.2. Radiotherapy-related characteristics

Fig. 1 illustrates the distribution of estimated absorbed dose metrics DMEAN and V5Gy for the complete heart and for the LAHW. The average DMEAN ± standard deviation (SD) of the complete heart was in the same range for cases (left-sided = 4.27 ± 1.57 Gy, right-sided = 1.64 ± 0.60 Gy) and controls (left-sided = 4.31 ± 1.74 Gy, right-sided = 1.66 ± 0.94 Gy). Doses for left-sided RT were much higher compared to doses for right-sided RT. The same observations apply to the average DMEAN of the LAHW (Table 2).

The supplementary information (Table A.1) presents patient characteristics of the 91 cases and 182 controls with observed individual dose from the dosimetry sample as well as the distribution of their doses (Table A.2 & Figure A.1). In general, the characteristics of cases and controls from the dosimetry sample (Table A.1) are in line with characteristics of those cases and controls of the complete group (Table 1). The predicted doses of the complete group correspond to the doses of the dosimetry sample, although they tend to be slightly higher.

3.3. Conditional logistic regression

We did not observe a linear dose-response relationship between DMEAN of the complete heart and risk for a cardiac event in the adjusted analyses (OR per 1 Gy increase = 0.99, 95% CI 0.94–1.05, $P = .72$). The same applies to the crude model. Analyses of dose categories did not reveal a monotonic trend with increasing dose categories, neither in crude nor in the adjusted analyses (Table 3). Adding a linear quadratic term to our dose-response model did not result in an improved model fit. Analyses of DMEAN of the LAHW did not reveal any dose-response relationship in the crude and adjusted model (OR per 1 Gy increase = 1.00, 95% CI 0.98–1.01, $P = .68$). The same holds for the categorical analyses (Table 3).

No increase in risk for a cardiac event was observed in association with the proportion of the complete heart that received more than 5 Gy (Table 4). The proportion of the LAHW receiving more than 5 Gy was not a significant risk factor (OR per 1% increase = 1.00, 95% CI 0.996–1.004, $P = .99$). We observed a small but statistically non-significant increased OR of 1.06 (95% CI 0.67–1.67, $P = .82$) in the

Table 1
Characteristics of cases and matched controls after breast cancer therapy in 1998–2008.

Characteristics	Cases		Controls	
	$N = 494$	100 (%[c])	$N = 988$	100 (%[c])
Year of breast cancer diagnosis				
1998–2000	62	12.55	129	13.06
2001–2003	94	19.03	182	18.42
2004–2006	213	43.12	441	44.64
2007–2008	125	25.30	236	23.89
Age at breast cancer diagnosis				
Mean	63.14	/	63.10	/
SD[a]	11.93	/	11.85	/
Laterality				
Left	264	53.44	540	54.66
Right	230	46.56	448	45.34
T-stage				
1	267	54.05	572	57.89
2	151	30.57	307	31.07
3	21	4.25	29	2.94
4	26	5.26	40	4.05
In situ	21	4.25	33	3.34
Unknown	8	1.62	7	0.71
N-stage				
0	311	62.96	586	59.31
1	111	22.47	248	25.10
2	34	6.88	77	7.79
3	15	3.04	45	4.55
X	23	4.66	32	3.24
BMI[b]				
<25.0	207	41.90	411	41.60
≥25.0	253	51.21	509	51.52
Unknown	34	6.88	68	6.88
History of cardiac disease[d]				
Yes	84	17.00	168	17.00
No/unknown	410	83.00	820	83.00
Chemotherapy				
Yes	215	43.52	398	40.28
No	276	55.87	576	58.30
Unknown	3	0.61	14	1.42
Endocrine therapy				
Yes	382	77.33	745	75.40
No	98	19.84	201	20.34
Unknown	14	2.83	42	4.25
Type of surgery				
None[e]	3	0.61	1	0.10
Breast conserving	425	86.23	843	85.32
Mastectomy	66	13.36	144	14.57
Unknown	0	0.00	0	0.00

[a] SD: Standard deviation.
[b] BMI: Body Mass Index.
[c] Percentages may not add up to a total of 100 due to rounding.
[d] History of cardiac disease at the time of breast cancer diagnosis, including history of cardiac infarction, coronary heart disease, angina pectoris, NYHA≥3, dysrhythmia, vitium cordis or use of a pacemaker.
[e] Patients who did not receive breast conserving surgery or mastectomy during their breast cancer therapy.

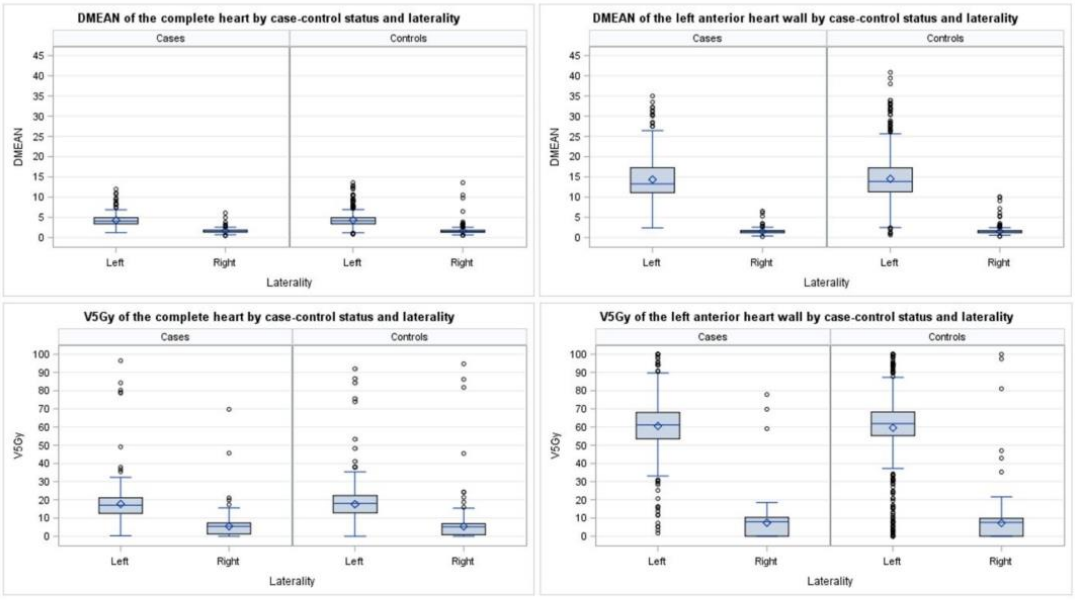

Fig. 1. Boxplots of estimated mean heart dose and V5Gy of 494 cases and 988 matched controls after breast cancer therapy in 1998–2008 depending on case-control status and laterality for the complete heart and the left anterior heart wall based on dose predictions using multiple imputation.

Table 2
Mean, median and standard deviations for the complete heart and left anterior heart wall for different exposure metrics for 494 cases and 988 matched controls after breast cancer therapy in 1998–2008 stratified by laterality based on dose predictions using multiple imputation.

Structure	Metric	Laterality	Mean		Median		SD		Range	
			Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Complete heart	DMEAN [Gy]	Left	4.27	4.31	4.08	4.15	1.57	1.74	1.21–11.98	0.80–13.56
		Right	1.64	1.66	1.57	1.50	0.60	0.94	0.44–6.10	0.56–13.56
	V5Gy [Gy]	Left	17.71	17.61	17.05	18.02	11.68	10.13	0.28–96.45	0–91.99
		Right	5.47	5.37	5.44	5.18	6.29	7.96	0–69.74	0–94.69
Left anterior heart wall	DMEAN [Gy]	Left	14.34	14.53	13.26	13.87	6.12	6.35	2.37–34.99	0.65–40.85
		Right	1.53	1.55	1.44	1.39	0.70	0.91	0.23–6.51	0.30–10.09
	V5Gy [Gy]	Left	60.57	59.54	61.25	61.87	17.86	19.26	1.68–100	0–100
		Right	7.40	7.22	7.96	7.59	8.70	9.04	0–77.82	0–100

categorical analyses for the category 10%–29% of the LAHW receiving more than 5Gy compared to the reference category (<10%). Crude ORs were in line with the adjusted ORs (Table 4).

Sensitivity analyses restricted to cases and their corresponding controls with available individual dose information did not alter the results of the main analysis (Table A.3 & Table A.4). No significant increased risk for cardiac events was observed, neither for the complete heart nor for the LAHW. This observation applies to both dose metrics, DMEAN and V5Gy.

4. Discussion

4.1. Main results

We assessed the risk for cardiac events after RT in female BC patients treated between 1998 and 2008 in Germany with a nested case-control analysis including 494 cases and 988 controls. We did not observe a significantly increased risk for cardiac events per Gy increase of DMEAN to the complete heart or LAHW in BC patients. Additional multivariable conditional logistic regression revealed no evidence for an increased risk for cardiac events associated with V5Gy for the complete heart or the LAHW.

4.2. Comparison to earlier studies

Our findings are generally supported by recent studies that used tumor laterality as a surrogate measure, showing no significantly increased risk for cardiac late effects for more recent treatment periods including 1998–2008 [19], 1999–2006 [28], 2000–2008 [29], 2000–2009 [30], 2001–2005 [31]. In addition, our results are in line with two recently published large clinical trials with long-term follow-up [32,33]. After a median follow-up of 15.7 years [32] and 34 years [33] no increased risk for cardiac death was observed comparing patients randomly assigned to lymph node radiation [32], or chestwall and regional lymph node radiation after mastectomy [33], respectively. However, studies based on individual dosimetry yield different results. Darby et al. [12] reported a linear increase for rates of major coronary events of 7.4% (95% CI 2.9–14.5, $P < .001$) per 1 Gy mean dose to the complete heart for patients treated between 1958 and 2001. In an update of the Danish part of Darby et al. an increased risk of 19% (95% CI

Table 3
Conditional logistic regression analyses of potential risk factors associated with cardiac morbidity and cardiac mortality of 494 cases and 988 matched controls after breast cancer therapy in 1998–2008.

Variables	Crude			Adjusted†		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Dose groups for complete heart using DMEAN [Gy]						
1st quintile (<1.24 Gy)	1.00[a]			1.00[a]		
2nd quintile (≥1.24 Gy - <1.87 Gy)	1.00	0.63–1.58	.99	0.99	0.63–1.58	.98
3rd quintile (≥1.87 Gy - <2.84 Gy)	1.02	0.66–1.56	.93	1.01	0.66–1.55	.96
4th quintile (≥2.84 Gy - <4.60 Gy)	1.02	0.62–1.68	.94	1.01	0.61–1.67	.96
5th quintile (≥4.60 Gy)	1.00	0.64–1.55	.99	0.99	0.64–1.54	.97
Complete heart using DMEAN [Gy], continuous per 1 Gy	0.99	0.94–1.05	.73	0.99	0.94–1.05	.72
Dose groups for left anterior heart wall using DMEAN [Gy]						
1st quintile (<1.11 Gy)	1.00[a]			1.00[a]		
2nd quintile (≥1.11 Gy - <2.37 Gy)	1.00	0.64–1.55	.98	0.98	0.63–1.53	.94
3rd quintile (≥2.37 Gy - <7.38 Gy)	1.06	0.68–1.66	.80	1.05	0.67–1.66	.82
4th quintile (≥7.38 Gy - <15.12)	0.94	0.61–1.43	.76	0.94	0.61–1.42	.76
5th quintile (≥15.12 Gy)	0.94	0.62–1.42	.76	0.93	0.62–1.41	.74
Left anterior heart wall using DMEAN [Gy], continuous per 1 Gy	1.00	0.98–1.01	.68	1.00	0.98–1.01	.68
Chemotherapy						
No	1.00[a]			1.00[a]		
Yes	1.18	0.93–1.50	.18	1.20	0.94–1.54	.15
Endocrine therapy						
No	1.00[a]			1.00[a]		
Yes	1.05	0.80–1.39	.72	1.09	0.82–1.45	.61
BMI[b]						
<25.0	1.00[a]			1.00[a]		
≥25.0	0.99	0.78–1.24	.91	0.98	0.78–1.24	.89

† Radiation-related factors are adjusted for chemotherapy, endocrine therapy and BMI. Chemotherapy, endocrine therapy and BMI are adjusted for each other and DMEAN of the complete heart as continuous variable.
[a] Reference category.
[b] BMI: Body Mass Index.

Table 4
Conditional logistic regression analyses of percentage of heart volume receiving >5 Gy and cardiac morbidity and cardiac mortality of 494 cases and 988 matched controls after breast cancer therapy in 1998–2008.

Variables	Crude			Adjusted[b]		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Groups of percentage of the complete heart receiving >5 Gy [V5Gy]						
<10%	1.00[a]			1.00[a]		
10%–29%	1.01	0.76–1.35	.95	1.00	0.75–1.34	.99
≥30%	0.94	0.60–1.46	.78	0.94	0.60–1.47	.78
Percentage of the complete heart receiving >5 Gy [V5Gy], continuous per 1%	1.00	0.99–1.01	.96	1.00	0.99–1.01	.98
Groups of percentage of the left anterior heart wall receiving >5 Gy [V5Gy]						
<10%	1.00[a]			1.00[a]		
10%–29%	1.06	0.67–1.67	.80	1.06	0.67–1.67	.82
≥30%	1.02	0.79–1.31	.90	1.02	0.79–1.32	.88
Percentage of the left anterior heart wall receiving >5 Gy [V5Gy], continuous per 1%	1.00	0.996–1.004	.99	1.00	0.996–1.004	.99

[a] Reference category.
[b] Adjusted for chemotherapy, endocrine therapy and BMI.

1%–63%, $P = .02$) per Gy of MHD for major coronary events was reported [34]. Jacobse et al. [18] observed a linearly increasing risk for myocardial infarctions of 6.4% per Gy MHD to the complete heart (95% CI 1.3%–16.0%) in patients treated between 1970 and 2009. For V5Gy and myocardial infarction, the authors identified a statistically significant increased risk for V5Gy ≥ 30% of the complete heart (RR 2.02, 95% CI 1.43–2.85, $P = .008$). In a cohort study of 910 BC patients with RT in 2005–2008 in the Netherlands, 30 major cardiac events occurred [17]. This cohort study observed a 16.5% (95% CI 0.6%–35.0%, $P = .042$) increase of the cumulative incidence per Gy of radiation to the complete heart for major cardiac events [17]. A detailed overview of key characteristics and results of these mentioned studies including our study is presented in the supplementary information (Table A.5).

In contrast to these previous studies on individual dosimetry of RT, we did not observe a dose-dependent increase in risk for cardiac events. The MHD in our study were considerably lower than in Darby et al. [12] and Jacobse et al. [18]. Both used radiation therapy charts to reconstruct doses, which may reduce the reliability of reported doses. Our doses were comparable to van den Bogaard et al. [17], but higher than Lorenzen et al. [34] (Table A.5), who both also based their dosimetry on 3D-CT planning records like our study. Beside these discrepancies in MHD, several other systematic differences to previous studies may have contributed to our dissimilar results, namely differences with respect to the treatment period, the definition of the endpoint, and age restriction.

Most previous studies mainly included patients treated before 2000 [12,18,34], while 75% of our patients received RT between 2000 and 2008. Guidelines for RT in BC patients and RT techniques have changed over the years [5]. This led to a reduction of radiation dose to the heart. In addition, clinicians' awareness of potential cardiac effects due to RT may have increased over the years [35], contributing to treatment selection and reductions of heart dose. Therefore, comparison to earlier studies, which include patients from 1958 to mainly before 2000 is hampered.

We used a broader definition for the cardiac event endpoint compared to earlier studies with a more narrow endpoint, focused on only myocardial infarction [18] or on myocardial infarction, coronary revascularization and death from ischemic heart disease [12,17,34]. In our study, however, a wider range of cardiac morbidities like dysrhythmias or valvular heart disease were included. This might lead to an endpoint that is not significantly associated with heart dose compared to previous studies that used a more specific endpoint. However, as a post-hoc explorative analysis, we conducted separate analyses for the two endpoints cardiac mortality and cardiac morbidity (Table A.6). Despite a small, statistically non-significant increased risk for cardiac mortality associated with DMEAN of the complete heart (OR per 1% increase = 1.03, 95% CI 0.91–1.15, $P = .66$), the results were consistent with the results from the main endpoint of cardiac events.

In our study, 28% of patients were >70 years at time of diagnosis. In comparison, previous studies restricted age at diagnosis to <70 [12], <71 [18], or ≤75 [12,34]. A large cross-sectional study in Germany showed that the 12-month prevalence for myocardial infarction, chronic

consequences of myocardial infarction or angina pectoris substantially increases with age in women from 3.4% (55–64 years) to 16.0% (≥75 years) [36]. Therefore, the effect of RT on cardiac events might be diminished by inclusion of a substantial number of women aged 70 and older at time of diagnosis, who are at higher risk for a cardiac event due to their age regardless of differences in radiation dose due to RT.

4.3. Strength and limitations

Our study included a large number of cases and controls treated with contemporary 3D-conformal RT between 1998 and 2008 with extensive clinical documentation, including information on cardiac comorbidities at baseline. Evidence on cardiac risk based on individual dosimetry and comprehensive follow-up of patients from this treatment period is sparse internationally and completely missing for Germany so far, making our study an important contribution.

Despite these strengths, our study had limitations. Individual doses were only available for a subset of cases and controls since the heart was not completely visible in some CT scans, preventing heart dosimetry. In addition, for some patients, electronic treatment planning records were not accessible. Therefore, we performed dose predictions to estimate heart dose for cases and controls without individual dosimetry. Nevertheless, sensitivity analyses restricted to cases and controls with individual dosimetry did not reveal differences in risk estimates compared to the main analyses that included dose predictions. Furthermore, information on cardiac morbidity were derived from a self-administered questionnaire. This implies a risk for selection bias. Survivors with a healthy lifestyle might have been more motivated to participate in a questionnaire on late cardiac effects compared to non-responders. Additionally, self-reported events may be prone to information bias through restrictions in memory, misunderstanding of medical diagnoses, or selective reporting [37]. This could potentially result in misclassification. However, a validation study on a patient sample of our study demonstrated a moderate to fair agreement between self-reported events compared to medical records from general practitioners [38].

5. Conclusion

Our results provide no evidence that the radiation dose to the heart from contemporary 3D-conformal RT for female breast cancer patients treated between 1998 and 2008 is associated with cardiac events.

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Ethical approval

The ESCaRa Study has been approved by the Ethics Committee of Rhineland-Palatinate, Mainz and the Ethics Committee of the University of Ulm. The data protection officer approved using the patients' hospital records and the performing of a mortality follow-up for the entire cohort without written informed consent of the patients. For the questionnaire survey, individual informed consent was obtained.

Availability of data

Raw data compliant with the institutional confidentiality policies can be available upon request from the corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.05.007.

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5 Discussion

This cumulative PhD-thesis consists of two internationally published peer-reviewed articles. They provide an important contribution to the discussion of cardiac late effects in female breast cancer patients with 3D-conformal radiotherapy. Especially the dose-response analysis fills a hitherto existing research gap for Germany. Here, the main findings of the two articles are discussed, including strength and limitations of the studies. Lastly, an overall conclusion and outlook for potential further research is presented.

In Article I of this thesis [126] (Section 3), results for the risk of long-term cardiac mortality and cardiac morbidity in female breast cancer patients of the ESCaRa-Study based on tumour laterality as a proxy for cardiac dose due to radiotherapy are described. A total of 11,982 female breast cancer patients with treatment in 1998-2008 (Section 2.1, Figure 1) were included in the analysis. More than 75% of the included patients were treated after 2000 and the mean age at diagnosis was 60.9 years (range 18-101 years). Of the complete cohort 2,925 (24.4%) women did not receive radiotherapy and therefore were excluded from the analyses of tumour laterality. Among the other 9,057 patients with radiotherapy, left-sided and right-sided breast cancer was distributed nearly equally. The analysis on cardiac mortality revealed no statistically significant increased risk for left-sided vs. right-sided radiotherapy (HR 1.09, 95% CI 0.85-1.41). For cardiac morbidity no significant increased risk was observed for tumour laterality either (HR 1.05, 95% CI 0.88-1.25).

The results of Article I are generally in line with other international studies on long-term cardiac mortality in breast cancer patients with contemporary radiotherapy, which also used tumour laterality [110 112-114 116 117]. Compared to these other studies the median mortality follow-up of 11.1 years in Article I is comparatively long. Other studies are limited to a median mortality follow-up of <10 years. Concretely, median follow-ups vary between 4.6 years [114], 6.0 years [110], 6.4 years [116], 6.7 years (mean) [117], 7.7 years (mean) [112], and 8.8 years [113]. The authors of previous studies discussed their limited follow-ups as a significant source for uncertainty of their results. They uniformly reported no association of 3D-conformal radiotherapy and cardiac mortality in breast cancer patients, but their limited follow up has the potential to underestimate the actual risk. The risk estimates based on a distinctly longer follow-up as reported in Article I of this thesis therefore result in an important contribution to the body of evidence. Article I ensures the previous findings of international studies based on a large cohort with an up to more than twice as long median follow-up compared to single studies [114]. However, it cannot be ruled out that with an even longer follow-up, further cases of cardiac mortality might occur. This could influence the estimated risks for cardiac mortality due to 3D-conformal radiotherapy in breast cancer patients.

Studies on cardiac morbidity show conflicting results (Section 1.3.1). In short, a number of studies did reveal an increased risk for both older and more recent therapy regimes including the years 1989-2005 [118], 1977-1989 and 2001-2005 [119], 1999-2005 [121], and 1976-1989 and 1990 onwards [106]. While other studies did not show any association of tumour laterality and cardiac morbidity after radiotherapy for breast cancer for the years 1998-2008 [103], 2000-2009 [114], 1996-2010 [120], and 2008-2016 [121]. Similar to the analysis for cardiac mortality it cannot be ruled out, that a longer morbidity follow-up with more than a median of 12.4 years would lead to the inclusion of even more cases of cardiac disease. This could alter the estimated risks. In addition, some studies that did show an association used data of population based-registries to identify women with cardiac morbidity after radiotherapy for breast cancer [118 121]. In contrast, analysis on cardiac morbidity in Article I might be prone to self-selection bias as cardiac morbidity was assessed via a self-administered questionnaire instead of routine data or registry data [127]. Participants in the self-administered questionnaire may have been motivated in participating by a higher interest in cardiac effects after radiotherapy and generally have a healthier lifestyle. Vice versa, women with a poor health condition at the time of the questionnaire or generally less interest in health related topics may tend to reject participation [103]. However, other studies based on large register databases such as the SEER database [114] or the Danish population based registries [121], with a comparable therapy period also identified no effect of tumour laterality on cardiac morbidity. Whereas these studies are not prone to selection bias because of a systematic follow up via register data. In addition, although women participated in the self-administered questionnaire might not generally be representative for the complete cohort, the effect of tumour laterality on cardiac morbidity should not be affected by this, because using laterality can be considered as a quasi-randomized study design [103 106 116]. In contrast, a comparison of women that received radiotherapy vs. women without radiotherapy could have been significantly affected by this selection bias. Women with radiotherapy include a smaller proportion of CIS cancers (as shown in Table 1 of Article I [126]) and therefore are less likely to receive mastectomy without any adjuvant treatment. Additionally, the group of women without radiotherapy are also more likely to include patients with guideline violations in treatment due to e.g. advanced age or history of cardiac diseases at baseline (as shown in Table 1 of Article I [126]). Although selection bias should not influence the effect of tumour laterality on cardiac morbidity, it could be affected by the risk of information bias. Patients might not be informed about the specific type of heart disease and give incorrect answers in the self-administered questionnaire [128]. Restriction in memory, misunderstanding of medical diagnosis, or selective reporting could also appear. This could potentially results in misclassification [129]. It can be assumed that this misclassification is likely non-differential regarding tumour laterality, which might have led to an underestimation of the true effect [103]. However, a validation study on the agreement between patient self-reports and information from

physicians including a sample 1,212 women of the ESCaRa cohort revealed a moderate to fair agreement [130].

Strengths of Article I are the effective mortality follow-up with only 1.1% loss to follow-up and a comprehensive ascertainment of the causes of death with a completeness of 97%. Further strengths are the extensive clinical documentations of breast cancer patients treated in the ESCaRa-Study clinics and certified breast centers and a comparatively large number of observed cardiac events (240 cases of cardiac mortality and 497 cases of cardiac morbidity), which enables for statistical models including a broad range of potential confounders [126]. However, both the analysis on cardiac mortality and cardiac morbidity of Article I of this thesis [126] are united in the limitation of tumour laterality as a dose proxy.

Article II [129] contains results of a dose-response analyses based on a case-control study nested within the cohort of the ESCaRa-Study. In total, 494 women with 3D-conformal RT who subsequently developed a cardiac event and 988 controls were matched on year of breast cancer diagnosis, study center, and cardiac comorbidities at the time of breast cancer diagnosis. Over 75% of the cases and controls received radiotherapy treatment >2000. The retrospective dosimetry showed a mean dose to the heart of 4.27 Gy (1.21 Gy-11.98 Gy) for left-sided radiation in cases and 4.31 Gy (0.80 Gy-13.56 Gy) for controls and 1.64 Gy (0.44 Gy-6.10 Gy) and 1.66 Gy (0.56 Gy-13.56 Gy) for right-sided radiation, respectively. The dose-response analysis for DMEAN of the complete heart did not reveal any association with cardiac events (OR per 1 Gy increase 0.99, 95% CI 0.94-1.05, *p*=.72) nor a linear dose-response relationship. Likewise, the analysis of DMEAN for LAHW did not reveal any dose-response relationship for cardiac events (OR per 1 Gy increase 1.00, 95% CI 0.98-1.01, *p*=.68). Analyses for V5Gy for the complete heart (OR per 1% increase 1.00, 95% CI 0.99-1.01, *p*=.98) as well as for the LAHW (OR per 1% increase 1.02, 95% 0.79-1.32, *p*=.88) did not reveal any dose-response relationship either. Results were consistent across all analyses when comparing risk estimates and corresponding CI for adjusted and unadjusted models. Additional explorative analyses stratified for cardiac mortality and cardiac morbidity did likewise show no departure from the main analysis [129].

As described in detail in Article II of this thesis [129], the results are generally supported by studies that used tumour laterality as a proxy for cardiac dose and include more recent treatment periods [110 113-115]. However, the results of the dose-response analysis are not in line with previous studies that used individual dosimetry to estimate a potential dose-response relationship for radiotherapy in breast cancer patients and cardiac late effects. Previous studies using individual retrospective dosimetry of exposure to ionizing radiation to the heart reported a linear dose-response relationship for mean dose to the complete heart and cardiac late effects. These previous studies include female breast cancer patients from Sweden and

Denmark [76 122], and the Netherlands [82 123]. Three of these four studies are case-control studies [76 122 123] and one study is a cohort study [82]. The study by Darby et al. [76] is by far the largest study, including 963 cases and 1,205 controls. The nested case-control study of Article II of the ESCaRa cohort makes up for the second largest study including 494 cases and 988 controls, while other studies include 196 cases and 413 controls [122], 183 cases and 413 controls [123] and 30 cases in a cohort of 910 irradiated breast cancer patients [82]. The reported risk estimates for cardiac late effects in previous studies range from 6.4% increase per Gy MHD (95% CI 1.3-16.0) [123], 7.4% per Gy (95% CI 2.9-14.5), 16.5% per Gy (95 CI 0.6-35.0) to 19% increase per Gy (95% CI 1%-63%). For the alternative dose metric V5Gy, Jacobse et al. [123] did observe an increased rate ratio for myocardial infarction of 1.20 (95% CI 0.73-1.99) for 10%-29% of the volume of the complete heart being exposed to ≥5 Gy and a statistical significant increase of 2.02 (95% CI 1.43-2.85) for the highest category with ≥30% of the heart receiving ≥5 Gy [123]. Using the same categories for V5Gy in the corresponding analysis in Article II, no increased risk for cardiac events both for the complete heart and the LAHW was observed, including adjusted and crude analyses and sensitivity analyses restricted to women with individual de facto doses from the dosimetry sample [129]. In the analysis on V5Gy as a continuous variable the OR was 1.00 for both the complete heart (95% CI 0.99-1.01) and the LAHW (0.996-1.004) in Article II. Van den Bogaard et al. [82] did also report an analysis on V5Gy for the left ventricle, corresponding to the LAHW. In the univariate analysis they observed a statistically significant increased HR of 1.016 (95% CI 1.002-1.030) for acute cardiac events. However, the effect is small, the CI has borderline statistical significance, and the analysis is based on only 30 cases. These factors limit the reliability of their results.

A major difference between these previous studies on dose-response and the German study [129] of Article II, which may partly account for the discrepancy in risk estimates, is the difference in treatment years. While the previous studies mainly include treatment periods <2000, >75% of the included cases and controls in the German study [129] were treated >2000. This involves differences in treatment regimes and treatment planning [77] (Section 1.2.1), including a shift from conventional 2D radiotherapy to 3D-conformal radiotherapy based on CT scans. Additionally, an increase in awareness of potential cardiac late effects in radiation oncologist and clinicians must be taken into account. This awareness might be based on an increase in knowledge as a consequence of the first reports on potential cardiac late effects after radiotherapy of clinical trials with long-term follow-up in breast cancer patients by the EBCTCG [131]. This increased knowledge and awareness could then have resulted in a more heart sparing treatment [132], especially for women with cardiac comorbidities at baseline. This is partly supported by the differences in the MHD in two of the previous studies [76 123], including mainly radiotherapy regimes <2000 compared to

the German dose-response analysis of Article II. Median dose to the complete heart was 3.05 Gy for cases and 3.11 Gy for controls in the German dose-response analysis (4.30 Gy for left-sided irradiation and 1.65 Gy for right-sided irradiation) [129]. In contrast, Darby et al. [76] reported a MHD of 5.4 Gy for cases and 4.5 Gy for controls (6.6 Gy for left-sided irradiation and 2.9 Gy for right-sided irradiation). Jacobse et al. [123] observed a median dose to the complete heart of 8.9 Gy for cases and 8.5 Gy for controls. Both studies are not only based on older therapy regimes and treatment planning, they also used radiotherapy charts to reconstruct doses. This may reduce the reliability of reported doses compared to reconstructions based on CT images like in Article II [129]. However, doses of the German dose-response analysis [129] are comparable to those reported by van den Bogaard et al. [82] for the Netherlands (median of the MHD for cases 4.44 Gy and for controls 1.31 Gy) and higher compared to the doses reported by Lorenzen et al. [122] (median MHD 0.84 Gy for cases and 0.71 Gy for controls and 2.41 Gy for left-sided irradiation and 0.68 Gy for right-sided irradiation). Similar to the German study [129], these two studies based their retrospective dosimetry on 3D-CT planning records, which could indicate a more reliable retrospective dosimetry.

In Article II [129] further potential reasons for the contrasting results to previous studies are pointed out. A substantial part of the different results might be attributed to study heterogeneity, which hampers the comparability. In short, a broader definition for the cardiac event endpoint was applied in Article II. Previous studies used a narrower endpoint, focused only on myocardial infarction [123] or myocardial infarction, coronary revascularization and death from ischemic heart disease [76 82 122]. In Article II, however, a wider range of cardiac morbidities such as angina pectoris, congestive heart failure, dysrhythmias or valvular heart disease were also included beside the more common once such as myocardial infarction or ischemic heart disease. This might lead to an endpoint that is not significantly associated with heart dose compared to the previous studies that used a more specific endpoint. Nevertheless, a post-hoc explorative analysis, including separate analyses for the two endpoints cardiac mortality and cardiac morbidity, was conducted for the German study [129] in Article II. Despite a small, statistically non-significant increased risk for cardiac mortality associated with DMEAN of the complete heart (OR per 1% increase = 1.03, 95% CI 0.91–1.15, P = .66), the results were consistent with the results from the main endpoint of cardiac events [129]. Furthermore, in the German study [129] on dose-response, 28% of included patients were >70 years at the time of diagnosis. In comparison, most previous studies applied age restrictions for included patients. Age at diagnosis was restricted to <70 years [76], <71 years [123], or <75 years [76 122]. Only the study by van den Bogaard et al. [82] similarly applied no age restriction. However, the dose-response analysis of this study was based on a small number of cases (30 cases), resulting in a broad CI (0.6-35.0). Compared to the previous case-control studies [76 122 123], the matching criteria in the German study [129] were identical regarding age

and year of breast cancer diagnosis. In addition to these criteria, cardiac comorbidities at baseline and study center were used for matching in the German study [129]. Dose to the heart was shown to differ significantly between study centers in a previous subset of the dosimetry sample used in the German study [78]. Not including study centers as a matching variable might reduce the comparability of cases and controls due to differences in inter-center radiotherapy planning variability, patient selection and follow-up care. Previous case-control studies reported larger proportions of baseline cardiac risk in cases compared to controls, despite also having different definitions for baseline cardiac risk [76 122 123] (Supplementary Information, Table A.5), while in the German study [129] the proportion was equal due to matching. As baseline cardiac risk factors have a major influence on the risk for subsequent cardiac events [76 82 133], having more patients with these cardiac risk factors among cases compared to controls could influence the risk estimate. However, these previous studies reported stratified results according to presence or absence of baseline cardiac risk factors [76 123] or adjusted for it [82 122]. Furthermore, in the German study [129] a latency time of one year was applied, including only cases and controls from the underlying cohort with at least one year of follow-up in the analysis. Previous studies did not apply any latency period. Appling a one-year latency period results in a more conservative risk estimate by ensuring that there is a minimum amount of time between exposure and the onset of a cardiac late effect. Even though there is no established latency time for radiation and cardiac late effects in the literature, it can be assumed that the effects of radiotherapy will only become clinically apparent after longer periods of time [134 135], and most likely not within the first year after radiation. This is also supported by numerous epidemiological studies on cardiac late effects showing steeply increases in the risk for cardiac late effects with an increase of time since diagnosis of breast cancer [107].

Beside the aforementioned differences to previous studies on a potential dose-response relationship of radiotherapy in breast cancer patients and cardiac late effects, further limitations might have influenced the results of Article II, but could also partly have an impact on the analysis of tumour laterality of Article I. The ESCaRa cohort, and therefore also the nested case-control study consists of female breast cancer patients with treatment either at Mainz University Medical Center, Ulm University Hospital or at one of 16 certified breast centers in the vicinity of Ulm. Although this makes the ESCaRa-Study clearly a multicenter study, no patients from other federal states than Rhineland-Palatinate and Baden-Württemberg were included. If one were to assume that there are systematic differences in therapy across Germany, the generalizability of the results of this thesis to the whole of Germany would be limited. Nevertheless, there are established guidelines on radiotherapy treatment of breast cancer in Germany (Section 1.2.4), which should contribute to a high homogeneity in treatment practice in Germany. In addition, considering the

standardization on using tangential megavoltage photon fields and electron or photon boosts, treatment should be comparable in other large medical centers in other parts of Germany [78]. On the flip side, in a dosimetry study on a sample of the ESCaRa cohort differences in cardiac dose between the two included medical centers were observed and interpreted as a result of individual department policies [78]. For this reason, it cannot be ruled out that there are treatment differences in other federal states and regions in Germany. Furthermore, only study centers were included who voluntarily agreed to participate. This potentially implies the risk of selection bias. Study centers with comparatively higher doses, because of e.g. the use of older equipment or a more lose guideline adherence, or generally not a good documentation of previous treatment planning, might have refused to participate in ESCaRa. Such a systematic undercoverage of study centers with potentially higher doses therefore could bias the results towards the null.

Another limitation that is only relevant for the dose-response analysis is the lack of actual individual doses for all included cases and controls. This issue and the way it was tackled is described in Article II [129]. In short, actual individual doses were only available for 91 cases and 182 controls of all 494 cases and 988 controls included in the analysis. There were several reasons for the lack of actual individual doses for all cases and controls. First, in some CT scans the heart was not completely visible, which made contouring of the heart and its substructures impossible and therefore preventing the retrospective heart dosimetry. Second, for some patients, the electronic treatment planning records were not accessible in the 16 certified breast centers. In the smaller breast centers, documentation of radiotherapy treatment planning was not as continuous and consistent as in the two university medical centers. This was especially the case when radiotherapy treatment planning systems changed. Additionally, some private practices also changed ownership, relocated, or closed. Put together, the lack of a continuous and consistent documentation resulted in missing appropriate information on radiotherapy treatment and for this reason prevented the individual retrospective dosimetry [129]. Third and finally, the dosimetry sample was independently sampled from the cases and control, although both the dosimetry sample and the cases and controls came from the same underlying cohort. Therefore, it was expected that only a certain intersection of women is part of both, the dosimetry sample and the drawn cases and controls. Although individual dosimetry for each patient based on individual CT scans would be preferable, multiple imputation using fully conditional specification [136 137] has been used to estimate missing information on DMEAN and V5Gy for the complete heart and the LAHW [129]. Assuming missing at random, a previously validated dose prediction model [105] based on year of breast cancer diagnosis, age at breast cancer diagnosis, laterality, BMI, and study center was used. In Article II [129] results of extensive sensitivity analyses

(Supplementary Information, Table A.1, A.2, A.3, A.4, Figure A.1) restricted to patients with dosimetry based on their individual electronic radiotherapy treatment planning records (91 cases and 182 controls) have been reported to enable a comparison to the analyses based on imputed information. The results of the sensitivity analysis are in line with the main analysis, that was based on multiple imputation of missing doses. This indicates that the multiple imputation did not introduce any significant error and thus strengthens the results. Further, residual confounding is another limitation of the dose-response analysis. Their might have been confounding factors such as socioeconomic status and modifiable lifestyle factors including physical activity, diet, or smoking that have not been taken into account. Although, in a previous analysis of tumour laterality of the PASSOS Heart Study, a sensitivity analysis for a subset of patients with available information on socioeconomic status and smoking (yes vs. no) was performed. Additional adjustment to these two factors did not alter the results [103]. The analysis of Article I however, should be in general less prone to residual confounding, due to its quasi-randomized design as tumour laterality is mostly random.

Strengths of Article II are the inclusion of a comparatively large number of cases and controls treated with contemporary 3D-conformal radiotherapy and the extensive clinical documentation, including information on cardiac comorbidities [129]. So far evidence on cardiac late effects based on individual dosimetry in combination with a comprehensive follow-up of patients from the treatment era after 2000 is sparse internationally and was completely missing for Germany before this work. In addition, in both articles of this thesis, a large set of confounders were included in the statistical models, including chemotherapy. Specific chemotherapy regimens have been considered cardiotoxic, namely anthracyclines such as doxorubicin [138 139]. However, chemotherapy in the statistical models of this thesis was included as a dichotomous variable indicating if a women received any chemotherapy treatment or not. It would have been of interest to include precise details of the chemotherapy, e.g. which therapeutic agent was used and information on the dose. Lorenzen et al. [122] and Jacobse et al. [123] for example took into account the general prescription of adjuvant chemotherapy, but also looked at chemotherapy type and differentiated between the prescription of anthracyclines and no anthracyclines. Nevertheless, both studies had only very few cases in the group of women with anthracyclines. The other two relevant previous studies [76 82] used a similar approach to the one used in this thesis.

In summary, despite the discussed limitations of Article I and Article II of this cumulative PhD-thesis, the results reassure the relatively safety of modern radiotherapy techniques. The findings suggest that 3D-conformal radiotherapy for female breast cancer is not associated with a significantly increased risk for cardiac late effects. This might be interpreted as a result of the extensive efforts to spare the heart as an

important OAR during radiotherapy, taking into account patient co-morbidities as well as chemotherapy, and providing follow-up care. As the results differ from previous international dose-response studies, more independent studies with a comparatively recent treatment period and long follow-up are needed to verify the findings. However, since the time of treatment period included in the ESCaRa-Study (1998-2008), further efforts were taken to further reduce the cardiac exposure during radiotherapy for breast cancer. This includes the modulation of dose, the ability to shape beams, block regions of the heart, make use of deep inspirational breath holds, and accurately position the patient during treatment (Section 1.2.3). If there would be a small but undetected risk for cardiac late effects due to the radiotherapy treatment regime investigated in this thesis, cardiac exposure to ionizing radiation might even be more reduced nowadays, potentially further reducing the risk for adverse outcomes [140].

The following options could be considered as an outlook for future research based on the ESCaRa-Study. First, in an explorative analysis other substructures of the heart and other dose metrics could be investigated. Through the dosimetry sample of ESCaRa information on individual doses to the aortic valve, pulmonary valve, the right anterior heart wall including the right coronary artery and sinoatrial node, and the atrioventricular node [78] are available. Additional alternative dose metrics to consider could be the relative volume exposed to at least 10 Gy (V10Gy) or the dose received by the maximally exposed 2 cm^3 (D2CC) [78]. Second, based on the CT images of the ESCaRa-Study a coronary artery calcium (CAC) score could be retrospectively determined to identify patients with a higher risk for coronary artery disease. Long before the onset of clinically significant cardiac late effects, subclinical cardiac changes might occur [124]. Identifying patients with high risk for radiation-induced cardiac complications through effective subclinical markers would be beneficial for primary and secondary prevention [124], making early detection of cardiovascular changes an interesting field of research. Currently, there are two ongoing prospective cohort studies on early detection and prediction of cardiovascular changes and cardiotoxicity in the first two years after 3D-conformal radiotherapy called the BACCARAT (BreAst Cancer and Cardiotoxicity Induced by Radio Therapy) prospective cohort study [141] and the MEDIRAD EARLY HEART Study [124]. Both studies include extensive clinical examinations on subclinical cardiac changes before the beginning of radiotherapy and during the course of the follow-up at various points in time. The clinical examinations include echocardiography for myocardial changes, assessment of a broad range of circulating biomarkers, and coronary computed tomography angiography (CCTA) for coronary changes. CCTA visualizes the coronary arteries and enables to detect early calcification, plaques and stenosis. Based on the images a CAC score is used to identify patients with a higher risk for coronary artery disease [124 141]. However, ESCaRa is a retrospective cohort study, which does not allow for this prospective approach. Nevertheless, in a

Dutch study by Roos et al. [133] the CAC score was retrospectively assessed via CT scans, which are routinely used for radiotherapy treatment planning. Based on an association model Roos et al. [133] described the relationship between the CAC score and acute coronary events after correction for confounding factors [133]. With the available CT scans in ESCaRa, a similar approach would be feasible to retrospectively assess the CAC. This would provide additional new evidence on cardiac effects in breast cancer patients after 3D-conformal radiotherapy from this cohort. Third, to increase the number of events and enable to assess more robust effect estimates one could add additional years of follow-up by a continuation of the systematic individual mortality follow-up and an additional questionnaire on cardiac morbidity. Alternatively, and potentially even more useful, a pooled analysis based on original data of the previous studies including data of the ESCaRa dose-response study with individual retrospective dosimetry on cardiac late effects after radiotherapy in female breast cancer patients could be conducted. This approach would combine several benefits at the same time. The main advantage would be the increased statistical power due to the larger sample size, which leads to more precise risk estimates. Additionally, in a pooled analysis harmonization in terms of inclusion and exclusion criteria, outcome definition, exposure categories, and other sources of heterogeneity, which are extensively pointed out in Article II [129] and the discussion of this thesis (Section 5), is feasible. Differences in statistical risk analysis methods could be harmonized too, as different methods could hamper the comparability of results of the single studies [142]. A first step to this approach would be to assess the general willingness of the principal investigators of the previous studies to participate in such a pooling project.

Appendix

A Supplementary information on Article I: Cardiac late effects after modern radiotherapy in breast cancer patients - a retrospective cohort study in Germany (ESCaRa)

Supplementary Information, SI 1

Short questionnaire on cardiac illness and on cardiovascular risk factors

Did a physician ever diagnose one of the following diseases? (multiple answers possible)			**If yes, when did you get the diagnosis for the first time?** (Please, indicate age **or** calendar year)	
	No	Yes	Age	Calendar Year
Myocardial infarction	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Angina pectoris	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Congestive heart failure (ischemic heart disease)	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Arrhythmia of the heart	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Valvular heart disease	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Stroke	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Diabetes mellitus	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Hypertension	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Obesity, overweight	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Increased blood cholesterol, increased blood lipids	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Chronic Lung Disease (Asthma, Bronchitis, Chronic obstructive pulmonary disease	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Chronic kidney disease	☐	☐	|__||__| Year	|__|__|__|__| (Year)
Thyroid functional disease	☐	☐	|__||__| Year	|__|__|__|__| (Year)

Did you have a pacemaker? No, don’t know, yes, if yes-when (calendar year)?

Did you have a stent implantation? No, don’t know, yes, if yes-when (calendar year)?

Was a balloon dilatation done? No, don’t know, yes, if yes-when (calendar year)?

Was a pass surgery done? No, don’t know, yes, if yes-when (calendar year)?

Supplementary Information, SI 2

Multivariate Cox Regression: cardiac mortality risk in breast cancer patients with radiotherapy and stratified for duration of follow-up with follow-up censored at the time of diagnosis of a recurrent event

			Duration of follow-up			
	All[a]		**>=1-<=10 years[b]**		**>10 years[c]**	
	HR	95% CI	HR	95% CI	HR	95% CI
RT, left vs. right	1.09	(0.84-1.41)	0.97	(0.70-1.34)	1.41	(0.91-2.17)
Age at diagnosis	1.21	(1.19-1.23)*****	1.15	(1.12-1.18)*****	1.21	(1.17-1.25)*****
Year of diagnosis	1.02	(0.96-1.08)	0.86	(0.81-0.91)*****	1.15	(1.01-1.30)
Cardiac history (yes/no)	1.42	(1.03-1.97)*****	1.00	(0.64-1.56)	1.79	(1.07-2.99)*****
Chemotherapy (yes/no)	1.16	(0.82-1.65)	0.90	(0.56-1.45)	1.50	(0.89-2.52)
Endocrine therapy (yes/no)	1.10	(0.78-1.56)	0.94	(0.62-1.42)	1.62	(0.85-3.11)
BMI coefficient 1**	0.97	(0.84-1.11)	0.95	(0.81-1.11)	1.02	(0.81-1.30)
BMI coefficient 2	1.01	(0.93-1.10)	1.02	(0.94-1.12)	0.94	(0.82-1.09)
BMI coefficient 3	0.99	(0.86-1.15)	0.97	(0.83-1.13)	1.12	(0.86-1.45)

Abbreviations: BMI, Body Mass Index; 95% CI, 95% Confidence Interval; HR, Hazard Ratio; RT, radiotherapy

[a]Analysis based on 8,856 and n = 235 cases of cardiac mortality
[b]Analysis based on N 2,452 individuals with 150 cases of cardiac mortality;
[c]Analysis based on N 6,404 and 85 cases of cardiac mortality;

***** statistically significant
** BMI coefficient: adjustments for BMI by using restricted cubic splines with 4 internal knots

Supplementary Information, SI 3

Multivariate Cox Regression: cardiac mortality risk in breast cancer patients with radiotherapy and stratified for duration of follow-up, based on a complete case-analysis

			Duration of follow-up			
	All[a]		**>=1-<=10 years[b]**		**>10 years[c]**	
	HR	95% CI	HR	95% CI	HR	95% CI
RT, left vs. right	1.10	(0.84-1.45)	1.04	(0.73-1.47)	1.33	(0.85-2.07)
Age at diagnosis	1.22	(1.20-1.25)*****	1.16	(1.13-1.18)*****	1.24	(1.20-1.29)*****
Year of diagnosis	1.01	(0.95-1.08)	0.85	(0.80-0.91)*****	1.12	(0.98-1.27)
Cardiac history (yes/no)	1.42	(1.00-2.02)*****	0.79	(0.48-1.30)	2.18	(1.29-3.69)*****
Chemotherapy (yes/no)	1.20	(0.83-1.72)	0.88	(0.53-1.46)	1.70	(1.00-2.89)
Endocrine therapy (yes/no)	1.10	(0.79-1.64)	1.01	(0.66-1.56)	1.69	(0.88-3.26)
BMI coefficient 1**	0.97	(0.85-1.11)	0.94	(0.81-1.10)	1.02	(0.81-1.29)
BMI coefficient 2	1.01	(0.96-1.09)	1.02	(0.94-1.11)	0.95	(0.82-1.09)
BMI coefficient 3	1.00	(0.87-1.16)	0.98	(0.84-1.13)	1.12	(0.87-1.44)

Abbreviations: BMI, Body Mass Index; 95% CI, 95% Confidence Interval; HR, Hazard Ratio; RT, radiotherapy

[a] Analysis based on 8,007 and n = 214 cases of cardiac mortality
[b] Analysis based on N 2,221 individuals with 133 cases of cardiac mortality;
[c] Analysis based on N 5,786 and 81 cases of cardiac mortality;

***** statistically significant
** BMI coefficient: adjustments for BMI by using restricted cubic splines with 4 internal knots

Supplementary Information, SI 4

Multivariate Cox Regression: overall mortality risk in breast cancer patients with radiotherapy for the ESCaRa cohort and stratified for duration of follow-up

			Duration of follow-up			
	All[a]		**>=1-<=10 years[b]**		**>10 years[c]**	
	HR	95% CI	HR	95% CI	HR	95% CI
RT, left vs. right	0.97	(0.90-1.05)	0.93	(0.85-1.02)	1.07	(0.92-1.26)
Age at diagnosis	1.06	(1.06-1.07)*****	1.03	(1.02-1.03)*****	1.09	(1.08-1.10)*****
Year of diagnosis	0.97	(0.96-0.99)*****	0.83	(0.81-0.84)*****	0.99	(0.95-1.03)
Cardiac history (yes/no)	1.21	(1.07-1.36)*****	0.87	(0.75-1.01)	1.22	(0.98-1.52)*****
Chemotherapy (yes/no)	1.51	(1.39-1.65)*****	1.52	(1.37-1.69)*****	1.31	(1.10-1.56)*****
Endocrine therapy (yes/no)	0.77	(0.70-0.85)*****	0.71	(0.64-0.79)*****	1.21	(0.98-1.50)
BMI coefficient 1**	0.96	(0.92-1.00)	1.01	(0.97-1.05)	0.95	(0.88-1.02)
BMI coefficient 2	1.02	(1.00-1.05)	1.00	(0.97-1.02)	1.02	(0.97-1.07)
BMI coefficient 3	0.97	(0.93-1.01)	1.01	(0.97-1.05)	0.98	(0.90-1.07)

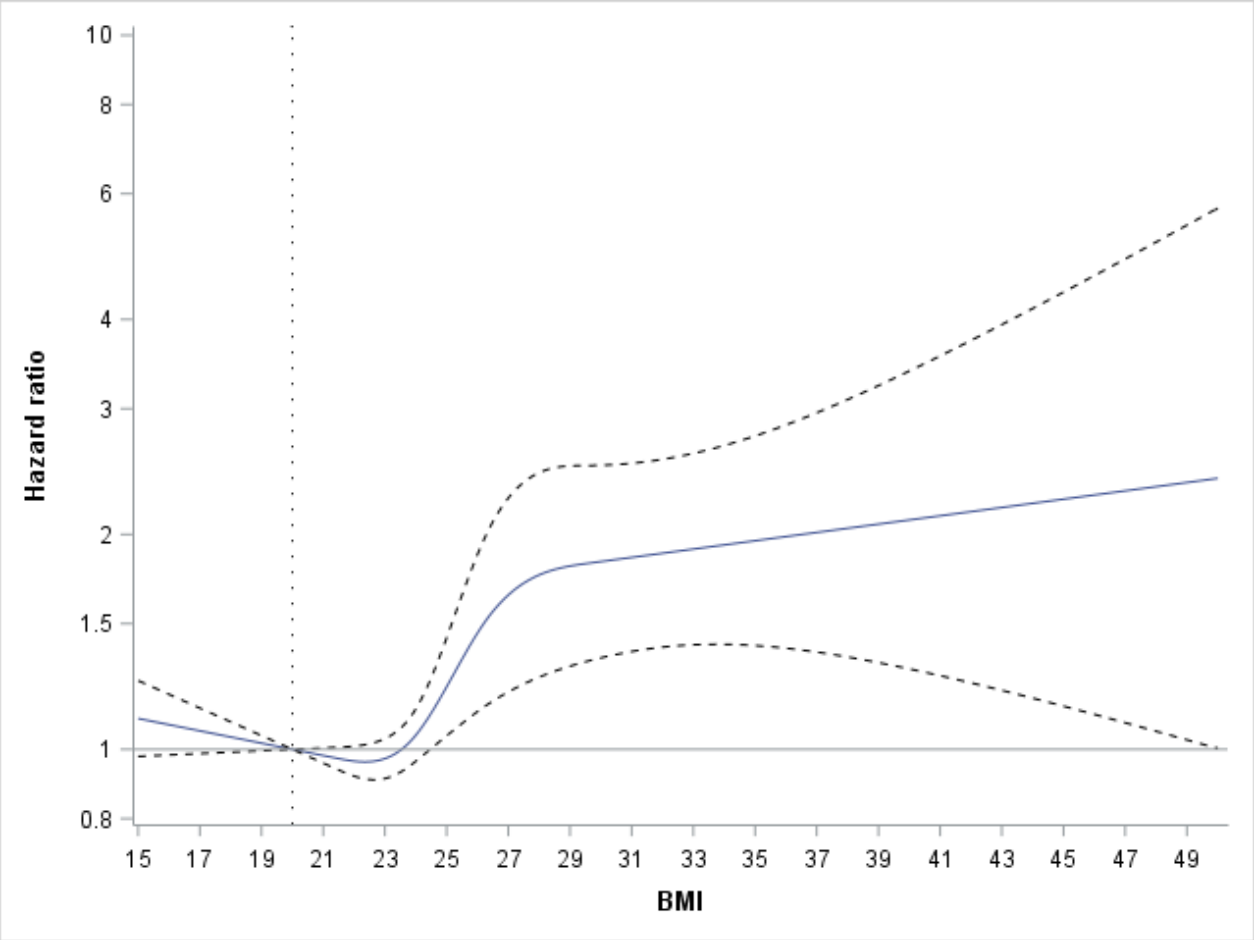
Abbreviations: BMI, Body Mass Index; 95% CI, 95% Confidence Interval; HR, Hazard Ratio; RT, radiotherapy

[a]Analysis based on 8,982 patients: total cohort (N=11,982) with at least one-year follow-up (11,719), with radiotherapy (8,982); n = 2460 cases of death
[b]Analysis based on N 2539 and 1833 cases of death
[c]Analysis based on N 6443 and 627 cases of death

***** statistically significant
** BMI coefficient: adjustments for BMI by using restricted cubic splines with 4 internal knots

Supplementary Information, SI 5

Marginal plot of BMI at time of breast cancer diagnosis using restricted cubic splines with 4 internal knots plotted against Hazard Ratios for cardiac mortality risk in breast cancer patients with radiotherapy (all other covariates were held constant)



Abbreviation: BMI, Body Mass Index;

Dashed lines: 95% confidence intervals

B Supplementary information on Article II: A nested case-control study on radiation dose-response for cardiac events in breast cancer patients in Germany

Supplementary Information, Table A.1

Characteristics of 91 cases and 182 matched controls after breast cancer therapy in 1998–2008 with available doses from the dosimetry sample

Characteristics	**Cases**		**Controls**	
	N = 91	100 (%†)	*N* = 182	100 (%†)
Year of breast cancer diagnosis				
1998–2000	22	24.18	47	25.82
2001–2003	22	24.18	46	25.27
2004–2006	27	29.67	59	32.42
2007–2008	20	21.98	30	16.48
Age at breast cancer diagnosis				
Mean	64.09	/	64.07	/
SD*	11.23	/	11.15	/
Laterality				
Left	55	60.44	101	55.49
Right	36	39.56	81	44.51
T-stage				
1	56	61.54	99	54.40
2	23	25.27	58	31.87
3	3	3.30	4	2.20
4	5	5.49	10	5.49
In situ	3	3.30	9	4.95
Unknown	1	1.10	2	1.10
N-stage				
0	63	69.23	109	59.89
1	22	24.18	54	29.67
2	2	2.20	5	3.30
3	2	2.20	7	3.85
X	2	2.20	6	3.30
BMI**				
<25.0	35	38.46	86	47.25
≥25.0	49	53.85	89	48.90
Unknown	7	7.69	7	3.85
History of cardiac disease‡				
Yes	35	38.46	70	38.46
No/unknown	56	61.54	112	61.54
Chemotherapy				
Yes	39	42.86	74	40.66
No	52	57.14	102	56.04
Unknown	0	0.00	6	3.30
Endocrine therapy				

Yes	69	75.82	120	65.93
No	18	19.78	43	23.62
Unknown	4	4.40	19	10.44
Type of surgery				
None§	0	0.00	1	0.55
Breast conserving	85	93.41	157	86.26
Mastectomy	6	6.59	24	13.19
Unknown	0	0.00	0	0.00

* SD: Standard deviation ** BMI: Body Mass Index

† Percentages may not add up to a total of 100 due to rounding.

‡ History of cardiac disease at the time of breast cancer diagnosis, including history of cardiac infarction, coronary heart disease, angina pectoris, NYHA≥3, dysrhythmia, vitium cordis or use of a pacemaker.

§ Patients who did not receive breast conserving surgery or mastectomy during their breast cancer therapy.

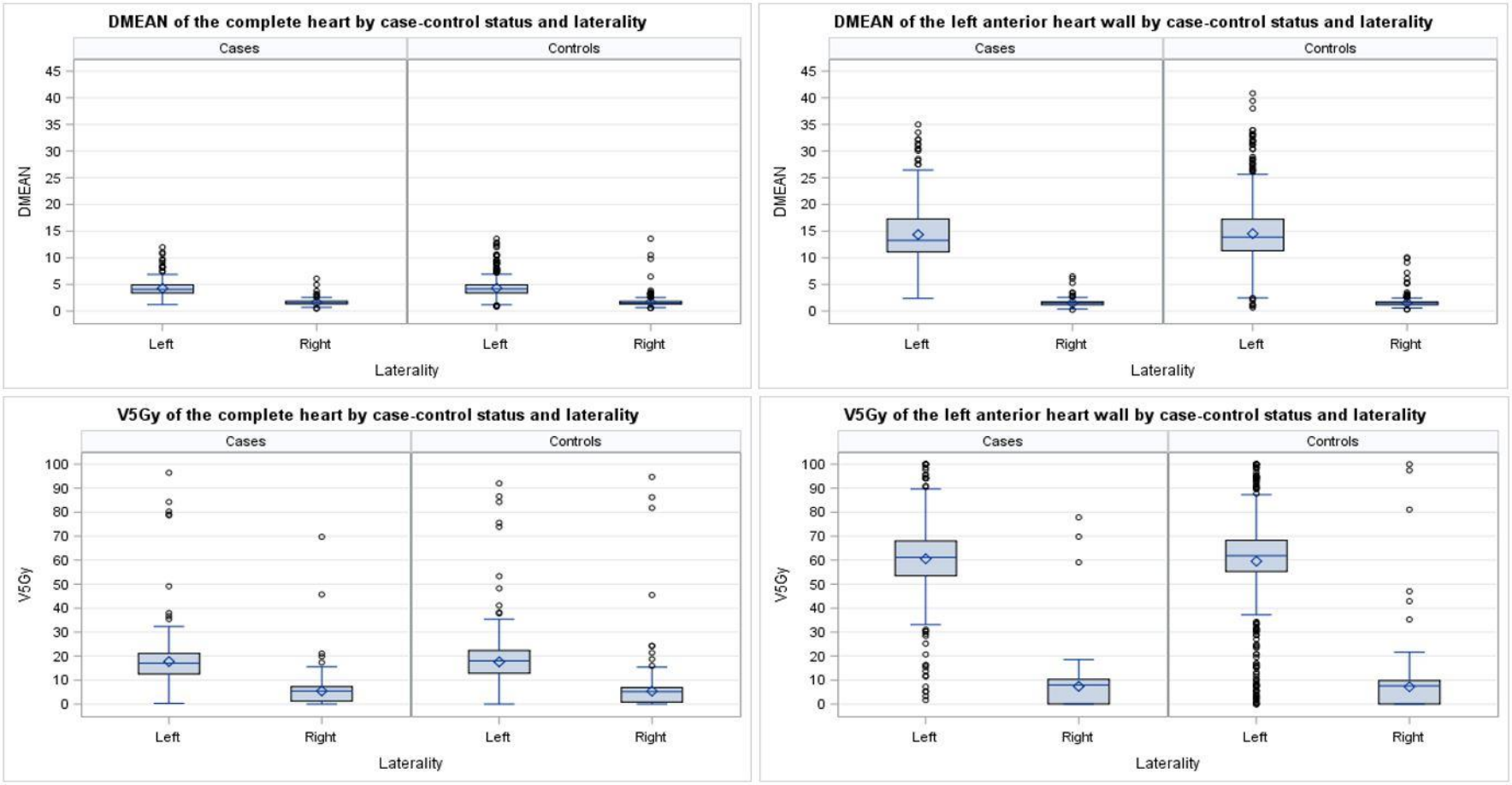
Supplementary Information, Table A.2

Mean, median and standard deviations for the complete heart and left anterior heart wall for different exposure metrics for cases and matched controls after breast cancer therapy in 1998–2008 stratified by laterality based on 91 cases and 182 controls with available doses from the dosimetry sample

Structure	Metric	Laterality	Mean		Median		SD		Range	
			Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Complete heart	DMEAN [Gy]	Left	3.92	4.38	3.30	3.89	2.13	2.70	1.21–10.75	1.00–12.85
		Right	1.59	1.70	1.47	1.46	0.73	1.15	0.54–3.77	0.56–9.79
	V5Gy [Gy]	Left	12.28	13.31	9.93	11.32	9.39	12.35	0.28–37.99	0–84.25
		Right	2.61	3.12	0	0	5.12	7.29	0–19.89	0–45.52
Left anterior heart wall	DMEAN [Gy]	Left	13.76	15.16	11.70	13.29	8.83	9.95	2.37–34.99	0.96–40.85
		Right	1.35	1.56	1.20	1.29	0.63	1.06	0.23–3.39	0.30–7.18
	V5Gy [Gy]	Left	57.26	55.64	57.34	61.94	25.77	30.58	3.28–95.36	0–100.
		Right	0.59	1.89	0	0	2.07	7.11	0–10.37	0–47.02

Supplementary Information, Figure A.1

Boxplots of estimated mean heart dose and V5Gy of cases and matched controls after breast cancer therapy in 1998–2008 depending on case-control status and laterality for the complete heart and the left anterior heart wall based on 91 cases and 182 controls with available doses from the dosimetry sample



The lines in the boxplots show the median and the rhombs show the mean.

Supplementary Information, Table A.3

Conditional logistic regression analyses of potential risk factors associated with cardiac morbidity and cardiac mortality of 91 cases and 182 controls after breast cancer therapy in 1998–2008 with available doses from the dosimetry sample

	Crude			Adjusted†		
Variables	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Dose groups for complete heart using DMEAN [Gy]						
1st quintile (<1.25 Gy)	1.00*			1.00*		
2nd quintile (≥1.25 Gy - <1.79 Gy)	0.96	0.41–2.25	.92	0.89	0.37–2.13	.79
3rd quintile (≥ 1.79 Gy - <2.71 Gy)	1.27	0.58–2.79	.56	1.25	0.56–2.79	.58
4th quintile (≥2.71 Gy - <4.73 Gy)	1.14	0.50–2.61	.75	1.07	0.46–2.47	.88
5th quintile (≥4.73 Gy)	1.07	0.47–2.42	.88	1.05	0.46–2.40	.91
Complete heart using DMEAN [Gy], continuous per 1 Gy	0.96	0.86–1.08	.52	0.96	0.86–1.08	.54
Dose groups for left anterior heart wall using DMEAN [Gy]						
1st quintile (<1.15 Gy)	1.00*			1.00*		
2nd quintile (≥1.15 Gy - <2.15 Gy)	0.92	0.38–2.22	.85	0.91	0.38–2.21	.84
3rd quintile (≥2.15 Gy - <7.56 Gy)	1.03	0.45–2.35	.95	1.06	0.45–2.49	.88
4th quintile (≥7.56 Gy - <18.07 Gy)	1.70	0.79–3.68	.17	1.63	0.75–3.53	.22
5th quintile (≥18.07 Gy)	0.70	0.29–1.68	.42	0.71	0.29–1.71	.44
Left anterior heart wall using DMEAN [Gy], continuous per 1 Gy	0.997	0.97–1.03	.83	0.997	0.97–1.03	.85
Chemotherapy						
No	1.00*			1.00*		
Yes	1.06	0.62–1.81	.83	1.12	0.64–1.97	.69
Endocrine therapy						
No	1.00*			1.00*		
Yes	1.37	0.75–2.51	.31	1.38	0.74–2.59	.32
BMI						
<25.0	1.00*			1.00*		
≥25.0	1.39	0.81–2.38	.23	1.36	0.79–2.34	.26

* Reference category.** BMI: Body Mass Index

† Radiation-related factors are adjusted for chemotherapy, endocrine therapy and BMI. Chemotherapy, endocrine therapy and BMI are adjusted for each other and DMEAN of the complete heart as continuous variable.

Supplementary Information, Table A.4

Conditional logistic regression analyses of percentage of heart volume receiving >5Gy and cardiac morbidity and cardiac mortality of 91 cases and 182 controls after breast cancer therapy in 1998–2008 with available doses from the dosimetry sample

	Crude			Adjusted†		
Variables	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Groups of percentage of the complete heart receiving >5 Gy [V5Gy]						
<10%	1.00*			1.00*		
10%-29%	0.94	0.54–1.63	.82	0.94	0.54–1.66	.83
≥30%	0.87	0.26–2.87	.82	0.82	0.24–2.80	.76
Percentage of the complete heart receiving >5 Gy [V5Gy], continuous per 1%	0.997	0.97–1.02	.81	0.998	0.97–1.02	.89
Groups of percentage of the left anterior heart wall receiving >5 Gy [V5Gy]						
<10%	1.00*			1.00*		
10%-29%	0.79	0.30–2.07	.62	0.79	0.29–2.10	.63
≥30%	1.43	0.83–2.46	.20	1.43	0.83–2.48	.20
Percentage of the left anterior heart wall receiving >5 Gy [V5Gy], continuous per 1%	1.003	0.96–1.01	.47	1.003	0.996–1.01	.47

*Reference category.

† Adjusted for chemotherapy, endocrine therapy and BMI.

Supplementary Information, Table A.5

Characteristics and results of case-control studies and cohort studies on female breast cancer patients with individual dosimetry of radiotherapy and risk for major cardiac events

Study characteristics	Darby et al., 2013	Van den Bogaard et al., 2017	Jacobse et al., 2019	Lorenzen et al., 2020	ESCaRa, 2022
Country	Sweden, Denmark	Netherlands	Netherlands	Denmark	Germany
Study type	Case-control	Cohort	Case-control	Case-control	Case-control
Cases/Controls*	963/1205	30/910	183/182	196/413	494/988
Treatment period	1958–2001 (Sweden), 1977–2000 (Denmark)	2005–2008	1970–2009 (<10% after 2000)	1977–2005	1998–2008 (>75% >2000)
Mean heart dose	Mean: Cases: 5.4 Gy Controls: 4.5 Gy Left: 6.6 Gy Right: 2.9 Gy	Median: Left: 4.44 Gy Right: 1.31 Gy	Median: Cases: 8.9 Gy Controls: 8.5 Gy	Median: Cases: 0.84 Gy Controls: 0.71 Gy Left: 2.41 Gy Right: 0.68 Gy	Median: Cases: 3.05 Gy Controls: 3.11 Gy Left: 4.30 Gy Right: 1.65 Gy
Endpoint	Myocardial infarction (I21–I24) Coronary revascularization Death from ischemic heart disease (I20–I25)	Myocardial infarction (I21–I24) Coronary revascularization Death from ischemic heart disease (I20–I25)	Myocardial infarction	Myocardial infarction (I21–I24) Coronary revascularization Death from ischemic heart disease (I20–I25)	Cardiac morbidity: Myocardial infarction, Angina pectoris, Congestive heart failure, Dysrhythmias, Valvular heart disease Cardiac mortality: Cardiac infarction (I21–I23), Chronic heart disease (I25.0–25.9), Acute ischemic heart disease (I21.0–24.9), Congestive heart failure (I50.0–I50.9), Angina pectoris (I20.0–I20.9), Cardiac arrest (I46), Dysrhythmias

					and conductive disorder (I44.0–I49.9), Vitium cordis (I34.0–37.9)
Inclusion criteria	Histologically confirmed breast cancer	Surgery Stage I-III invasive carcinoma or CIS	Stage I-III invasive carcinoma or CIS Surgery	Early stage breast cancer, Surgery	Histologically confirmed primary and locoregional breast cancer (invasive carcinoma or CIS)
Exclusion criteria	Bilateral breast cancer, Metastatic disease at time of breast cancer diagnosis, Prior cancer (apart from non-melanoma skin cancer) Prior radiotherapy to thoracic area	History of other malignant diseases Prior radiotherapy or chemotherapy before breast cancer	Prior cancer (apart from non-melanoma skin cancer) Breast cancer recurrence, Distant metastasis, Second cancer, Heart failure or valvular disease at MI diagnosis	Bilateral breast cancer, Unknown laterality, Prior cancer (apart from non-melanoma skin cancer) No radiotherapy for breast cancer	Bilateral breast cancer, Primary metastatic disease No radiotherapy for breast cancer
Age restriction	<70 years at diagnosis (Sweden), <75 years at diagnosis (Denmark)	No age restriction	<71 years at diagnosis	≤75 years at diagnosis	No age restriction (28% >70 at diagnosis)
Matching variables	Country of residence, Age and year of breast cancer diagnosis (both within 5 years), Receipt of radiotherapy, No recurrence of breast cancer, other cancer or major coronary event before index date	n.a.	Age and year of breast cancer diagnosis (both within 5 years)	Age and year of breast cancer diagnosis (both within 5 years), Time since radiotherapy (within 5 years)	Age and year of breast cancer diagnosis (both within 5 years), Study center, cardiac comorbidities

Latency time	No	No	No	No	1 year after breast cancer diagnosis
Age at diagnosis	Not available	Median: 59 years	Median Cases 50.2 years Controls 50.2 years	Median 62.5–63.6 years	Mean Cases 64.09 years Controls 64.07 years
Median follow-up	Not available	7.6 years	Cases 13.6 years Controls: 13.7 years	7.3–7.5 years	Cases: 12.52 years Controls: 12.76 years
Definition of baseline cardiac risk	Prior of ischemic heart disease, Risk factors other than ischemic heart disease: Circulatory disease, COPD, Smoking, BMI, Analgesic medication, Other medications (hormone replacement, thyroid, other)	Prior ischemic heart disease, Risk factors other than ischemic heart disease: circulatory disease, COPD, smoking, BMI, analgesic medication, other medications (hormone replacement, thyroid, other)	Prior cardiovascular diseases, Diabetes; Hypertension, Smoking, BMI	Prior myocardial infarction or angina pectoris, Prior circulatory diseases, Hypertension, Diabetes, COPD, Smoking, Obesity, Hormone replacement	Prior cardiac infarction, Coronary heart disease, Angina pectoris, NYHA ≥3, Dysrhythmia, Vitium cordis, Pacemaker
Occurrence of baseline cardiac risk	Cases: 63.3% Controls: 50.2%	More than one risk factor: 57.5%	Cases: 57.9% Controls: 44.5%	Prior myocardial infarction or angina pectoris: Cases 13.8% Controls: 2.4% Prior circulatory disease: Cases: 17.9% Controls: 14.5%	Cases: 17% Controls: 17%
Risk per Gy	7.4% increase per Gy (95% CI 2.9%–14.5%, *P* <0.001)	16.5% increase in cumulative incidence per Gy (95% CI 0.6%–35.0%, *P* 0.042)	6.4% increase per Gy (95% CI 1.3–16.0)	19% increase per Gy (95% CI 1%–63%, *P* 0.02)	OR 0.99 (95% CI 0.94–1.05, *P* 0.73)

* For cohort studies events and cohort size is reported

Supplementary Information, Table A.6

Conditional logistic regression analysis of risk for cardiac mortality and cardiac morbidity for exposure of the complete heart and exposure of the left anterior heart wall due to radiotherapy in female breast cancer patients treated between 1998-2008

	Cardiac mortality*			**Cardiac morbidity***		
Variables	Odds Ratio†	95% CI	*P*	Odds Ratio†	95% CI	*P*
Complete heart using DMEAN [Gy], continuous per 1 Gy	1.03	0.91-1.15	.66	0.98	0.92-1.04	.47
Percentage of the complete heart receiving >5 Gy [V5Gy], continuous per 1%	1.00	0.98-1.02	.86	1.00	0.99-1.01	.78
Left anterior heart wall using DMEAN [Gy], continuous per 1 Gy	1.00	0.97-1.04	.80	1.00	0.99-1.01	.78
Percentage of the left anterior heart wall receiving >5 Gy [V5Gy], continuous per 1%	1.00	0.99-1.01	.89	1.00	0.996-1.01	.86

* Analysis for cardiac mortality based on 105 cases and 210 controls; analysis of cardiac morbidity based on 389 cases and 778 controls

† Adjusted for chemotherapy, endocrine therapy and BMI.

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Curriculum vitae

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