

Opinion

Why Relative Survival of Breast Cancer Remains Flat?

Guy A Storme*

Department Radiation Oncology, UZ Brussel, Belgium

*Corresponding author

Guy A Storme, Department Radiation Oncology, UZ Brussel, Belgium, Tel: 32478872169.

Submitted: 14 September, 2025

Accepted: 23 October, 2025

Published: 27 October, 2025

ISSN: 2641-7685

Copyright

© 2025 Storme GA, et al.

OPEN ACCESS

Abstract

Numerous studies are offering novel medications for patients with breast cancer and reporting improvements in survival. Although the trials are well-described, at least 50% of patients are excluded because they are limited to those under 65 and free of co-morbidities. Even though there have been a ton of publications over the past two decades detailing how new chemicals are enhancing survival, the influence on Relative Survival (RS) has not been seen. Examining closely, the rise in Cardiovascular Deaths (CVDs) among people over 65 may be the cause. This reaffirms that additional non-cancer-related factors should be considered, as breast cancer is not the sole factor that affects patient outcomes. It is increasingly evident that patients with co-morbidities ought to be enrolled in clinical trials and/or that patients on those new medications need to be regularly watched, both of which raise the expense.

Keywords

- Breast Cancer
- Relative Survival
- Cardio-Vascular Death
- Drugs
- Surgery
- Radiotherapy

INTRODUCTION

A number of social economic status factors, including unemployment, low family income, food insecurity, homelessness, and single status, as well as behavioral factors, such as current smoking, a lack of leisure-time physical activity, and sleep patterns that involve fewer than or more than eight hours of sleep per day, all influence the risk of Cardiovascular Disease (CVD) [1,2]. However, age remains the most relevant predictor, particularly after the age of 65, and the risk has increased over the last 30 years [3]. Post-treatment radiation is the primary cause of cardiovascular illness in breast cancer patients, with an average of 1.58 from 1973 to 1982, 1.27 from 1983 to 1992, and 0.96 (95% CI = 0.82-1.12) from 1993 to 2001. For ten years, none of them were tracked [4]. In a recent study [5], Van de Steene et al., found no negative impact as radiation had a significant survival advantage ($2P < 0.05$), within large trials ($2P < 0.03$), with favourable crude survival ($2P < 0.03$), as with trials utilizing traditional fractionation ($2P < 0.02$). People with a history of cardiovascular illness are more likely than others to die of breast cancer within the first five years [6]. On July 25, 2016, Henson withdrew his EBCTRG (Early Breast Cancer Treatment Research Group) publication without explanation, citing differences in the results of meta-analyses of randomized trials and observational data from SEER registries [7]. The emphasis

was once again on radiotherapy-dead individuals, and disparities between the SEER and EBCTRG data were identified. The majority of patients in the Darby et al., study got systemic treatment alongside or in addition to radiotherapy after surgery. Numerous recent studies have indicated that radiotherapy's effects must be considered in conjunction with other therapies, as well as any pretreatment co-morbidities. The American Heart Association (AHA) found a high association and conducted a thorough examination of the significant overlap between heart disease and breast cancer [8]. We review here numerous factors that influence how radiotherapy and other treatments affect cardiovascular disease in breast cancer patients.

TUMOR SPECIFICATIONS

Tumor size (T classification) affects prognosis in BC patients as higher N classifications [9]. In T1a and b N0 M0 tumors, other characteristics, such as the combination of poor nuclear grade and lymphatic vascular invasion, define a very small subset (10%) with poor recurrence-free survival (RFS). Histologic grade, as measured by light microscopy and digital imaging, significantly predicts breast cancer specific survival (BCSS) and distant metastasis free survival (DMFS), with even greater prognostic significance [10,11], than gene signatures [12]. The likelihood of cardiovascular death in breast cancer

patients receiving chemotherapy or radiotherapy was linked to tumor size and stage [13].

TREATMENT

Treatment is stage-based, with higher stages requiring a combination of surgery, radiation, and systemic treatments, each of which has an impact on cancer outcome.

Surgery

Surgery is recommended as the first line of treatment in stages I, II, and III. In stages III, neoadjuvant systemic treatment may be used to shrink the tumor.

Breast conserving treatment (BCT) has a higher disease-free and overall survival rate than mastectomy, and the value of radiation therapy is commonly ignored [14,15].

Adjuvant radiation protects patients with early-stage breast cancer against recurrence and improves survival rates. Although this survival effect was formerly thought to as unfavourable, randomized studies highlight the importance of radiotherapy as part of breast cancer treatment [16]. A meta-analysis of over 1,500,000 patients found that breast conserving treatment with radiotherapy improved overall survival when compared to mastectomy [17]. Although radiation was previously linked to increased cardiac toxicity (see introduction), breast conserving treatment has recently been found to significantly lower heart-related mortality when compared to mastectomy [18]. Smaller tumors (T1-2) require less systemic treatment when breast conserving treatment is continued as an intervention, and the influence of breast conserving treatment on cardiovascular disease is overstated (see Systemic therapy). Paravertebral anesthesia and analgesia combined with general anesthesia outperformed general anesthesia combined with postoperative morphine analgesia in terms of recurrence and metastasis-free survival at 24 and 36 months [19,20]. This shows that the type of anesthetic may have an effect on breast cancer outcomes. In contrast, in a randomized clinical trial, regional anesthetic (propofol and paravertebral block) did not diminish breast cancer recurrence after potentially curative surgery when compared to volatile anesthesia (sevoflurane) and opioids [21].

Radiotherapy

Darby and colleagues discovered a proportionate relationship between ischemic heart disease and the mean radiation dose to the heart, which they calculated to be 7.4% per gray (Gy) beginning in the first five years and increasing until twenty years later, with the highest statistical events

occurring in left-irradiated breast tumors, due to more heart tissue in the radiation field. Patients with a history of ischemia heart illness have a much greater prevalence [6,7]. This also holds for individuals with additional co-morbid diseases such as diabetes, chronic lung illness, other circulatory disorders, female smoking, a high BMI, or painkiller use.

When compared to the left anterior descending coronary artery, the apparent mean dose to the heart was a better predictor of major coronary events. Except for a history of heart issues, cardiovascular disease did not appear to be associated with any other risk factors [22]. In an earlier publication (2011), not cited by Darby et al. (2013), tumor classification (T, N), location (right or left, outer or inner quadrant), and patient age (older versus young) all had an effect on breast cancer mortality, but no excess cardiac mortality could be attributed to radiation therapy. On the contrary, radiation reduces both relapse free survival and total survival [23].

Although some previous studies [24-26], reported an increase in cardiovascular mortality among those receiving radiation therapy, other studies [27,28], found no effect on cardiovascular illness. Radiation therapy to the left side of the chest wall may harm the neighbouring arteries or the heart muscle, increasing the risk of cardiovascular disease. However, multiple previous investigations found no significant difference in cardiac events among patients receiving radiation for either left or right-sided malignancies [29-31]. The fact that modern radiation treatments are more focused and less cardiotoxic than older ones may explain these later results, as well as other recent findings unrelated to cardiovascular disease [32].

Age, co-morbidities

The risk of fatal heart disease increases with age in almost all cancer survivors [33], and the standard mortality ratio (SMR) from older cancer patients within a year of receiving chemotherapy (CT) is approximately five times higher than that of patients who did not receive chemotherapy or radiotherapy. Even after ten years, the typical mortality ratio for individuals dying from cardiovascular disease with chemotherapy plus irradiation remains twice that of patients receiving radiation therapy alone [34]. Rapid advances in our understanding of the biology of aging have brought new insights on a variety of serious age-related diseases [35]. In the United States, two major public health concerns are cardiovascular disease and breast cancer, both of which cause significant morbidity and mortality in women. Although breast cancer survival rates have improved significantly as a result of thorough screening

and tailored treatment, significant cardiotoxic side effects remain [36]. Cancer patients' survival is heavily influenced by their age. Between 2009 and 2013, nine European countries evaluated four common breast cancer therapies: mastectomy, breast-conserving surgery plus radiation therapy (BCS + RT), mastectomy reconstruction, and fast treatment (within six weeks after diagnosis). Mastectomy patients had more comorbidities and were older than those undergoing breast-conserving surgery ($p < 0.001$). Breast reconstruction (25% of mastectomies) was associated with younger women and lower comorbidities ($p < 0.001$). Women who received early treatment (45%) were younger ($p = 0.001$) and less likely to have comorbidities ($p < 0.001$). According to this investigation, conventional treatment was rarely provided to older patients [37]. When it comes to heart-related survival, age is the major cause of death for people over 70, but surgical approaches also play a role [38]. Cardiovascular mortality is a significant competing risk cardiovascular mortality for women over the age of 66 with early-stage breast cancer. Following early-stage breast cancer treatment, ischemic heart disease is the leading cause of hospitalization for cardiovascular illness [39]. The increased frequency of hospitalization prompts us to evaluate various co-morbidities associated with older people, which may have a competing effect with breast cancer as the leading cause of death. The fully adjusted relative hazards of the effects of comorbidities on breast cancer-specific mortality were 1° 1.24 (95% confidence interval [CI] 1.13 to 1.26) for cardiovascular disease, 2° 1.13 (95% CI 1.13 to 1.26) for prior cancer, 3° 1.13 (95% CI 1.05 to 1.22) for chronic obstructive pulmonary disease, and 4° 1.10 (95% CI 1.03 to 1.16) for diabetes [40]. In the first five years after a previous episode of cardiovascular illness, the risk of dying from cardiovascular disease is comparable for patients with a history of breast cancer; afterward, death from cardiovascular disease became more common [41]. Heart disease predominantly kills the elderly, whereas cancer primarily kills middle-aged and young women [42]. The oncologic team must weigh the risks and advantages of various treatments and drugs that interact with cardiac function and may cause cardiovascular disease, potentially affecting long-term survival [43]. The evidence of shared risks and pathways between cancer and cardiovascular disease has recently been evaluated [44]. Without statistics on hospitalizations for all causes, authorities struggle to establish the net benefit of a treatment. Almost one out of every two heart failure trials that report hospitalizations for heart failure do not include hospitalizations for all reasons [45].

Systemic Treatment

In the 1980s, anthracycline (DOX) became a crucial

component of breast cancer adjuvant therapy. When all systemic therapies were used concurrently, 5-year recurrence rates were significantly reduced, but 5-year mortality rates were only modestly reduced [46]. When anthracycline was administered to patients with breast cancer, there was early evidence of cardiotoxicity, which was dose-dependent [47,48]. Epirubicin, which is less toxic and can be administered at doses nearly three times greater than DOX, reduces cardiac toxicity while maintaining the same good outcome [49].

The literature shows that women aged 66 to 70 who received adjuvant anthracyclines had a significantly increased incidence of congestive heart failure. Over more than ten years of follow-up, the disparity in congestive heart failure rates widened [50].

DOX causes substantial cardiotoxicity, and its therapeutic index is limited. Damage from oxidative stress and DOX are caused by distinct processes [51]. Myocardial toxicity can be caused by an imbalance of endogenous antioxidants and reactive oxygen species (ROS) in response to damage [52]. DOX-induced tissue damage includes changes in the vascular matrix and loss of endothelial regulation of vascular smooth muscle cell tone due to reduced nitric oxide generation [53].

These changes may cause acute structural vascular problems. When DOX treatment begins, echocardiography and multi-gated acquisition scanning are employed to validate heart function prior to each DOX dosage. These tests determine the Left Ventricular Ejection Fraction (LVEF), which is utilized to avoid myocardial dysfunction. Cardiotoxicity is most commonly related with age and pre-existing left ventricular failure. Other cardiovascular diseases, such as arterial hypertension and coronary artery disease, have been associated to an elevated risk of cardiotoxicity in diabetic patients [54]. Lanza's study [55], summarizes all chemotherapy medicines that interfere with cardiac function, whether alone or in combination.

In comparison to other systemic treatments, heart failure is a common side effect of trastuzumab therapy for older women, with rates greater than those seen in most clinical studies. After three years, the effect of adding anthracycline to trastuzumab is around 21.7% [56], which is greater than in clinical trials, which typically select people under the age of 65 with no heart disease antecedents [57]. Women with breast cancer who were matched with cancer-free women had a consistently higher risk of several cardiovascular illnesses [58]. Breast cancer survivors are more likely than other women to die from cardiovascular disease. More than five years

after cancer diagnosis, there are still increased risks of arrhythmia, heart failure, pericarditis, and deep vein thrombosis, which, even when properly managed, can lead to cardiovascular death [59]. Comorbidity is a major contributor to both overall and cancer-specific mortality among breast cancer survivors. In general, older patients who have co-morbidities that increase with age are more likely to die [60]. It is widely acknowledged that cancer medications have a stronger impact on cardiovascular disease, particularly in the elderly [61]. Women who have received adjuvant chemotherapy at the appropriate doses for breast cancer are found to be in menopause, which raises the risk of cardiovascular disease [62-64].

Other chemotherapeutic agents that affect cardiovascular disease include 5-fluorouracil (5-Fu), which can cause coronary vasospasm [65], taxanes, which can stimulate endothelial nitric oxide synthase (54 and 67) by increasing arterial stiffness in vascular endothelial cells, and cyclophosphamide, which, at high doses, can cause irreversible heart failure [66]. Since the advent of tamoxifen, hormone receptor-positive breast tumors have shown a decrease in recurrence and increased survival. Furthermore, there is evidence that aromatase inhibitors increase the incidence of vascular disease compared to tamoxifen, which could be attributable to the latter's preventative effect [67]. Tamoxifen, on the other hand, has been linked to an increased number of major venous thromboembolic events, including pulmonary embolism and deep vein thrombosis [68,69].

Although aromatase inhibitors raised the risk of myocardial infarction and stroke, as well as heart rate failure and CV mortality, they were deemed to be more effective than tamoxifen [70]. Long-term tamoxifen treatment does not appear to increase overall survival in patients with primary, recurring, or contralateral breast cancer.

Indeed, unfavorable side effects such as an increased incidence of thromboembolic events or uterine cancer may have a net negative impact [71].

The usage of CDK4/6 inhibitors resulted in myocardial infarction (12.9%), cardiac problem (12.1%), atrial fibrillation (12.9%), palpitation (10.1%), and heart failure (8.5%), with ribociclib causing the most of these events at a median of 69 days of treatment [72]. Three CDK4/6 inhibitors have recently been used in clinical practice and have demonstrated relatively consistent progression-free survival findings, while inconsistencies have appeared in their overall survival rates [73]. Even while abemaciclib paired with an NSAID resulted in a clinically relevant

increase in median overall survival over the NSAID alone, statistical significance was not achieved. Abemaciclib is not examined alone, therefore it is similar to testing a new medicine against an inactive rather than an active comparator, which may overestimate treatment outcomes [74]. Obesity is more common in postmenopausal women and has been linked to increased risk and poorer outcomes in breast cancer. It may also alter treatment options due to numerous molecular factors [75].

Obesity can have both direct and indirect consequences, depending on how the heart reacts to the excess weight and whether it coexists with other illnesses such as diabetes or hypertension. Obesity (at 18 years) is inversely related to the risk of premenopausal (35 to 64 years) breast cancer [76]. Obesity disrupts cellular metabolism, including breast cancer in postmenopausal women with elevated estrogen levels. There is evidence that a link between diabetes and metabolic pathways influences tumor cells' interactions with their microenvironment [77].

Women with Type 2 diabetes were shown to have a greater risk of developing breast cancer, a link that became stronger when characteristics including body mass index and menopausal status were taken into account [78].

Diabetes and hyperglycemia did not promote cell proliferation in tumor xenograft models, but they did induce phenotypes similar to mesenchymal and stem cells, which are associated with increased motility and metastasis, as well as DNA repair failure [79]. Individuals with breast cancer are more likely to be overweight or obese, according to their body mass index (BMI). A BMI of 40 was associated with poorer overall results in breast cancer patients [80,81]. Diet and food diversity affect gut microorganisms, which play a role in the development of cardiovascular disease.

Through the production of bioactive metabolites such bile acids, SCFA (short-chain fatty acids), and TMA (trimethylamine)/TMAO (trimethylamine N-oxide), the gut microbiota functions as an endocrine organ and significantly influences host behavior and disease through a variety of ways. As many other diseases approach, gut microbes and metabolic pathways are becoming more and more appealing as possible targets for cardiovascular disease [82].

Newly developed drugs for breast cancer had virtually no effect on relative survival between 2000 and 2018 [83]. The study population is frequently limited to lower-risk individuals due to eligibility requirements for ongoing cancer clinical trials, which may not adequately reflect the larger patient population outside of the study [84].

Patients with metastatic or advanced cancer treated at practices with higher NQF 0210 rates (the percentage of cancer patients who received chemotherapy and died during the last 14 days of their lives) do not appear to have different survival rates [85].

Most cancer drugs, approved quickly, did not demonstrate increases in overall survival or quality of life within five years. Even when the rapid approval process is used, patients should be properly informed about cancer treatments that do not ultimately show improvements in patient-centered clinical outcomes [86]. Small, rapid, single-center trials evaluating a new drug may overestimate treatment outcomes when compared to an inactive comparator instead of an active one.

Clinical trial data collection, access, and use procedures have not evolved significantly over time, resulting in a disjointed and inefficient system that limits the amount and quality of evidence that may be generated [87].

Among older adults with diabetes, chronic obstructive pulmonary disease, and cardiovascular disease, cardiovascular disease was the leading cause of death in the research population [88]. This makes it challenging to assess the true benefits to the population at a cost that increased threefold between 2013 and 2017 [89].

Oncologists, cardiologists, primary care physicians, and pharmacists must work together to treat the underlying cause of heart disease using even the best techniques and drugs available in order to maximize the therapeutic effect of cancer treatment while minimizing competing cardiovascular toxicities in patients with hypertension and/or ischemic heart disease [90,91]. Despite the large number of new drugs even, medicare, a program providing medical care for the aged, conciliation is one important topic that is frequently ignored. Monitoring by pharmacists showed that oncologists initially missed more than half of the medications that were banned or closely monitored [92]. Finally, we might even ask what's the effect of all those new medications without any effect on RS, because from 2004 to 2021, despite SEER data revealing more favorable patients with higher local (55%-65.9%), fewer regional (30%-26.3%), and more HR+ (60%-70%) favorable cancers we should expect increase of RS [93]. The rationale is simple: no trial has used RS as an endpoint, and RS is comparing cancer patients' survival to the predicted survival in the general population, corrected for age and gender, which provides the true value of the effect of treatment. It is often used in registry-based research (e.g., SEER) to contextualize survival outcomes and provide the true effect on a population level, rather

than selected and or individual patients, and to waive other surrogate evaluation points such as metastatic- or event-free survival, pathologic complete response or time to progression. Using population relative survival should also avoid quick approvals, which are rarely validated and skip long- term toxicology testing. All this is confirmed in the paper by Cheria et al about clinical trial uncertainties with new cancer drugs in journal publications and clinical guidelines [94].

CONCLUSION

Every patient should be involved in studies; if that isn't feasible, then at least the patients should be fully informed and treated solely in accordance with the "new drugs" inclusion criteria. Every doctor who prescribes medication should understand medicare conciliation, and cardiovascular evaluation should be given more careful consideration.

Marie Curie once said: "People who don't care about the past aren't deserving of the future".

REFERENCES

1. He J, Bundy J, Geng S, Tian L, He H, Li X, et al. Social, Behavioral, and Metabolic Risk Factors and Racial Disparities in Cardiovascular Disease Mortality in U.S. Adults : An Observational Study. *Ann Intern Med.* 2023; 176: 1200-1208.
2. Zhang YB, Chen C, Pan XF, Guo J, Li Y, Franco OH, et al. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. *BMJ.* 2021; 373: n604.
3. Zhao D, Wang Y, Wong N, Wang J. Impact of Aging on Cardiovascular Diseases From Chronological Observation to Biological Insights: JACC Family Series. *JACC Asia.* 2024; 4: 345-358.
4. Darby S, MacGale P, Taylor C, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol.* 2005; 6: 557-565.
5. Van de Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. *Radiother Oncol.* 2000; 55: 263-272.
6. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A Population-Based Study of Cardiovascular Mortality Following Early- Stage Breast Cancer *JAMA Cardiol.* 2017; 2: 88-93.
7. Henson KE, Jagsi R, Cutter D, McGale P, Taylor C, Darby S. Inferring the Effects of Cancer Treatment: Divergent Results From Early Breast Cancer Trialists' Collaborative Group Meta-Analyses of Randomized Trials and Observational Data From SEER Registries. *J Clin Oncol.* 2016; 34: 803-880.
8. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al. Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. *Circulation.* 2018; 137: e30-e66.
9. Liu Y, He M, Zuo WJ, Hao S, Wang ZH, Shao ZM. Tumor size still impacts prognosis in breast cancer with extensive nodal involvement. *Front Oncol.* 2021; 11: 585613.

10. Leitner SP, Swern AS, Weinberger D, Duncan L, Hutter R. Predictors of Recurrence for Patients with Small (One Centimeter or Less) Localized Breast Cancer (T1a,b NOMO). *CANCER*. 1995; 76: 2266-2274.
11. Rakha EA, Aleskandarani M, Toss MS, Green AR, Ball G, Ellis IO, et al. Breast cancer histologic grading using digital microscopy: concordance and outcome association. *J Clin Pathol*. 2018; 71: 680-686..
12. Alaeikhanehshir S, Ajayi T, Duijnhoven FH, Poncet C, Olaniran RO, Lips EH, et al. Locoregional Breast Cancer Recurrence in the European Organisation for Research and Treatment of Cancer 10041/BIG 03-04 MINDACT Trial: Analysis of Risk Factors Including the 70-Gene Signature. *J Clin Oncol*. 2024; 42: 1124-1134.
13. Chi K, LUO Z, Zhao H, Li Y, Liang y, Xiao Z, et al. The impact of tumor characteristics on cardiovascular disease death in breast cancer patients with CT or RT: a population-based study. *Front Cardiovasc Med*. 2023; 10: 1149633.
14. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of Breast Conservation Therapy vs Mastectomy on Disease-Specific Survival for Early-Stage Breast Cancer. *JAMA Surg*. 2014; 149: 267-274.
15. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011; 378: 1707-1716.
16. Guidolin K, Lock M, Vogt K, McClure J, Winick-Ng J, Vinden C, et al. Recurrence and mortality after breast-conserving surgery without radiation. *Curr Oncol*. 2019; 26: 380-388.
17. De la Cruz Ku G, Karamchandani M, Chambergo-Michilot D, Narvaez-Rojas AR, Jonczyk M, Principe-Meneses FS, et al. Does Breast-Conserving Surgery with Radiotherapy have a Better Survival than Mastectomy? A Meta-Analysis of More than 1,500,000 Patients. *Ann Surg Oncol*. 2022; 29: 6163-6188.
18. Li Z, Zhao R. Breast conservation therapy decreased heart- specific mortality in breast cancer patients compared with mastectomy. *BMC Surg*. 2023; 23: 233.
19. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiol*. 2006; 105: 660-664.
20. Zhang J, Chang CL, Lu CY, Chen HM, Wu SY. Paravertebral block in regional anesthesia with propofol sedation reduces locoregional recurrence in patients with breast cancer receiving breast conservative surgery compared with volatile inhalational without propofol in general anesthesia. *Biomed Pharmacother*. 2021; 142: 111991.
21. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Breast Cancer Recurrence Collaboration. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet*. 2019; 394: 1807-1815.
22. Darby S, Ewertz M, McGale P, Bennet A, Blom-Goldman U, Brønnum D, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *N Engl J Med*. 2013; 368: 987-998.
23. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet*. 2011; 378: 1707-1716.
24. Wang W, O'Connell D, Stuart K, Boyages J. Analysis of 10-year cause-specific mortality of patients with breast cancer treated in New South Wales in 1995. *J Med Imaging Radiat Oncol*. 2011; 55: 516-525.
25. Doyle JJ, Neugut AI, Jacobson JS, Wang J, McBride R, Grann A, et al. Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2007; 68: 82-93.
26. Roychoudhuri R, Robinson D, Putcha V, Cuzick J, Darby S, Møller H. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. *BMC Cancer*. 2007; 7: 9.
27. Harris EE, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA, et al. Late cardiac mortality and morbidity in early- stage breast cancer patients after breast-conservation treatment. *J Clin Oncol*. 2006; 24: 4100-4106.
28. Jimenez RB, Wong SM, Johnson A, Lalani N, Hughes KS. The Association Between Cardiac Mortality and Adjuvant Radiation Therapy Among Older Patients with Stage I Estrogen Positive Breast Cancer: A Surveillance, Epidemiology, and End Results (SEER)-Based Study on Cardiac Mortality and Radiation Therapy. *Adv Radiat Oncol*. 2020; 6: 100633.
29. Jingu K, Umezawa R, Yamamoto T, Takahashi N, Suzuki YU, Kishida K, et al. Recent Postoperative Radiotherapy for Left-sided Breast Cancer Does Not Increase Mortality of Heart Disease in Asians or Pacific Islanders: SEER Database Analysis. *Anticancer Res*. 2023; 43: 3571-3577.
30. Nixon AJ, Manola J, Gelman R, Bornstein B, Abner A, Hetelekidis S, et al. No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol*. 1998; 16: 1374-1379.
31. Patt DA, Goodwin JS, Kuo YF, Freeman JL, Zhang DD, Buchholz TA, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol*. 2005; 23: 7475-7482.
32. Harris EE. Cardiac mortality and morbidity after breast cancer treatment. *Cancer Control*. 2008; 15: 120-129.
33. Stoltzfus KC, Zhang Y, Sturgeon K, Sinoway LI, Trifiletti D, Chincilli VM, et al. Fatal heart disease among cancer patients. *Nat Commun*. 2020; 11: 2011.
34. Agha A, Wang X, Wang M, Lehrer EJ, Horn SR, Rosenberg JC, et al. Long-Term Risk of Death From Heart Disease Among Breast Cancer Patients. *Front Cardiovasc Med*. 2022; 9: 784409.
35. Zhao D, Wang Y, Wong N, Wang J. Impact of Aging on Cardiovascular Diseases From Chronological Observation to Biological Insights: JACC Family Series. *JACC Asia*. 2024; 4: 345-358.
36. Xie Y, Collins WJ, Audeh MW, Shiao SL, Gottlieb RA, Goodman MT, et al. Breast Cancer Survivorship and Cardiovascular Disease: Emerging Approaches in Cardio-Oncology. *Curr Treat Options Cardiovasc Med*. 2015; 17: 60.
37. Minicozzi P, Van Eycken L, Molinier F, Innos K, Guevara M, Marcos-Gragera R, et al, European HR Working Group on breast cancer. Comorbidities, age and period of diagnosis influence treatment and outcomes in early breast cancer. *Int J Cancer*. 2019; 144: 2118-2127.
38. Li Z, Zhao R. Breast conservation therapy decreased heart- specific mortality in breast cancer patients compared with mastectomy. *BMC Surgery*. 2023; 23: 233.
39. Abdel-Qadir H, Thavendiranathan P, Austin P, Lee D, Amir E, Tu JV, et al. The Risk of Heart Failure and Other Cardiovascular; Hospitalizations After Early-Stage Breast Cancer: A Matched Cohort Study. *J Natl Cancer Inst*. 2019; 111: 854-862.

40. Patnaik JL, Byers T, DiGuseppi C, Dabelea D, Denberg T. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res.* 2011; 13: R64.
41. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A Population-Based Study of Cardiovascular Mortality Following Early- Stage Breast Cancer. *JAMA Cardiol.* 2017; 2: 88-93.
42. Pathak E. Is Heart Disease or Cancer the Leading Cause of Death in United States Women? *Womens Health Issues.* 2016; 26: 589-594.
43. Florescu DR, Nistor DE. Therapy-induced cardiotoxicity in breast cancer patients: a well-known yet unresolved problem. *DISCOVERIES.* 2019; 7: e89.
44. Wilcox N, Amit U, Reibel J, Berlin E, Howrll K, Ky B. Cardiovascular disease and cancer shared risk factors and mechanisms. *Nat Rev Cardiol.* 2024; 21: 617-631.
45. Sayed A, ElRefaei M, Awad K, Salah H, Mandrola J, Foy A. Heart Failure and All- Cause Hospitalizations in Patients With Heart Failure A Meta-Analysis. *JAMA Network Open.* 2024; 7: e2446684.
46. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15- year survival: An overview of the randomised trials. *Lancet.* 2005; 365: 1687-1717.
47. Buzdar AU, Marcus C, Smith TL, Blumenschein GR. Early and delayed clinical cardiotoxicity of doxorubicin. *Cancer.* 1985; 55: 2761-2765.
48. Camilli M, Cipolla CM, Dent S, Minotti G, Cardinale DM. Anthracycline Cardiotoxicity in Adult Cancer Patients: JACC: Cardio Oncology State-of-the-Art Review. *JACC Cardio Oncology.* 2024; 6: 655-677.
49. Jain KK, Casper ES, Geller NL, Hakes TB, Kaufman RJ, Currie V, et al. A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. *J Clin Oncol.* 1985; 3: 818-826.
50. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer full text links. *J Clin Oncol.* 2007; 25: 3808-3815.
51. Songbo M, Lang H, Xinyong C, Bin X, Ping Z, Liang S. Oxidative stress injury in doxorubicin-induced cardiotoxicity. *Toxicol Lett.* 2019; 307: 41-48.
52. Florescu M, Mihalcea D, Enescu OA, Radu E, Chirca A, Acasandrei AM, et al. Taxanes-induced cardiotoxicity is related to increased arterial stiffness and oxidative stress. *Eur Heart J.* 2013; 34: P3006.
53. Dhesi S, Chu MP, Blevins G, Paterson I, Larratt L, Oudit GY, et al. Cyclophosphamide Induced Cardiomyopathy: A Case Report, Review, and Recommendations for Management. *J Investig Med High Impact Case Rep.* 2013; 1: 2324709613480346.
54. Polonsky TS, DeCara JM. Risk factors for chemotherapy-related cardiac toxicity. *Curr Opin Cardiol.* 2019; 34: 283-288.
55. Lanza O, Ferrera A, Reale S, Solfanelli G, Petrungaro M, Tini Melato G, et al. New Insights on the Toxicity on Heart and Vessels of Breast Cancer Therapies. *Med Sci (Basel).* 2022; 10: 27.
56. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of Heart Failure or Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer. *J Am Coll Cardiol.* 2012; 60: 2504-2512.
57. Matthews AA, Peacock Hinton S, Stanway S, Lyon AR, Smeeth L, Bhaskaran K, et al. Risk of Cardiovascular Diseases Among Older Breast Cancer Survivors in the United States: A Matched Cohort Study. *J Natl Compr Canc Netw.* 2021; 19: 275-284.
58. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular Disease Mortality Among Breast Cancer Survivors. *Epidemiology.* 2016; 27: 6-13.
59. Ramin C, Schaeffer ML, Zheng Z, Connor AE, Hoffman-Bolton J, Lau B, et al. All-Cause and Cardiovascular Disease Mortality Among Breast Cancer Survivors in CLUE II, a Long-Standing Community-Based Cohort. *J Natl Cancer Inst.* 2021; 113: 137-145.
60. Patnaik JL, Byers T, DiGuseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res.* 2011; 13: R64.
61. Accordino MK, Neugut AI, Hershman DL. Cardiac effects of anticancer therapy in the elderly. *J Clin Oncol.* 2014; 32: 2654-2661.
62. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *N Engl J Med.* 1989; 321: 641-646.
63. Walshe JM, Denduluri N, Swain SM. Amenorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 2006; 24: 5769-5779.
64. Luwaert RJ, Descamps O, Majois F, Chaudron JM, Beauduin M. Coronary artery spasm induced by 5-fluorouracil. *Eur Heart J.* 1991; 12: 468-470.
65. Songbo M, Lang H, Xinyong C, Bin X, Ping Z, Liang S. Oxidative stress injury in doxorubicin-induced cardiotoxicity. *Toxicol Lett.* 2019; 307: 41-48.
66. Dhesi S, Chu MP, Blevins G, Paterson I, Larratt L, Oudit GY, et al. Cyclophosphamide Induced Cardiomyopathy: A Case Report, Review, and Recommendations for Management. *J Investig Med High Impact Case Rep.* 2013; 1: 2324709613480346.
67. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst.* 2001; 93: 684-690.
68. Matthews A, Stanway S, Farmer RE, Strongman H, Thomas S, Lyon AR, et al. Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: Systematic review. *BMJ.* 2018; 363: k3845.
69. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. *J Clin Oncol.* 1991; 9: 286-294.
70. Khosrow-Khavar F, Filion KB, Bouganim N, Suissa S, Azoulay L. Aromatase Inhibitors and the Risk of Cardiovascular Outcomes in Women with Breast Cancer: A Population-Based Cohort Study. *Circulation.* 2020; 141: 549-559.
71. Fisher B, Dignam J, Bryant J, Wolmark N. Five Versus More Than Five Years of Tamoxifen for Lymph Node- Negative Breast Cancer: Updated Findings From the National Surgical Adjuvant Breast and Bowel Project B-14 Randomized Trial. *J Natl Cancer Inst.* 2001; 93: 1493-1494.
72. Kim JH. Profiling the Cardiovascular Toxicities of CDK4/6 Inhibitors: A Real-World Pharmacovigilance Study. *Cancers.* 2024; 16: 2869.
73. Morrison L, Loibl S, Turner NC. The CDK4/6 inhibitor revolution - a game- changing era for breast cancer treatment. *Nat Rev Clin Oncol.* 2024; 21: 89-105.
74. Michaeli DT, Michaeli T, Albers S, Michaeli JC. Clinical trial design and treatment effects: a meta-analysis of randomised controlled and single-arm trials supporting 437 FDA approvals of cancer drugs and indications. *BMJ Evid Based Med.* 2024; 29: 333-341.

75. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and Adverse Breast Cancer Risk and Outcome: Mechanistic Insights and Strategies for Intervention. *CA Cancer J Clin.* 2017; 67: 378-397.
76. Berstad P, Coates RJ, Bernstein L, Folger SG, Malone KE, Marchbanks PA, et al. A case-control study of body mass index and breast cancer risk in white and African- American women. *Cancer Epidemiol Biomarkers Prev.* 2010; 19: 1532-1544.
77. Brown KA. Metabolic pathways in obesity-related breast cancer. *Nat Rev Endocrinol.* 2021; 17: 350-363.
78. Lu Y, Hajjar A, Cryns VL, Trentham-Dietz A, Gangnon RE, Heckman-Stoddard BM, et al. Breast cancer risk for women with diabetes and the impact of metformin: A meta-analysis. *Cancer Med.* 2023; 12: 11703-11718.
79. Panigrahi G, Candia J, Dorsey TH, Tang W, Ohara Y, Byun JS, et al. Diabetes-associated breast cancer is molecularly distinct and shows a DNA damage repair deficiency. *JCI Insight.* 2023; 8: e170105.
80. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *N Engl J Med.* 2003; 348: 1625-1638.
81. Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism.* 2019; 92: 98-107.
82. Luqman A, Hassan A, Ullah M, Naseem S, Ullah M, Zhang L, et al. Role of the intestinal microbiome and its therapeutic intervention in cardiovascular disorder. *Front Immunol.* 2024; 15: 1321395.
83. Storme GA. Breast Cancer: Impact of New Treatments? *Cancers.* 2023; 15: 2205.
84. Jin S, Pazdur R, Sridhara R. Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015. *J Clin Oncol.* 2017; 35: 3745-3752.
85. Iskander R, Moyer H, Vigneault K, Mahmud SM, Kimmelman J. Survival Benefit Associated With Participation in Clinical Trials of Anticancer Drugs: A Systematic Review and Meta-Analysis. *JAMA.* 2024; 331: 2105-2113.
86. Liu ITT, Kesselheim AS, Cliff ERS. Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval. *JAMA.* 2024; 331: 1471-1479.
87. Joseph B, Franklin J, Marra C, Abebe K, Butte A, Cook D, et al. JAMA Summit on Clinical Trials Participants. Modernizing the Data Infrastructure for Clinical Research to Meet Evolving Demands for Evidence. *JAMA.* 2024; 332: 1378-1385.
88. Patnaik JL, Byers T, DiGuseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res.* 2011; 13: R64.
89. Neyt M, Devos C, Thiry N, Silversmit G, De Gendt C, Van Damme N, et al. Belgian observational survival data (incidence years 2004–2017) and expenditure for innovative oncology drugs in twelve cancer indications. *Eur J Cancer.* 2023; 182: 23-37.
90. Cohen JB, Brown NJ, Brown SA, Dent S, van Dorst DCH, Herrmann SM, et al; American Heart Association Council on Hypertension; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and Council on the Kidney in Cardiovascular Disease. Cancer Therapy-Related Hypertension: A Scientific Statement from the American Heart Association. *Hypertension.* 2023; 80: e46-e57.
91. Virani S, Newby K. 2023 AHA/ACC/ACCP/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary Disease. *JACC VOL.* 2023; 2: 833-955.
92. Malifarge L, Deppenweiler M, Italiano A, Lortal B. Impact of Medication Reconciliation in Oncology Early Phase Studies: A Drug-Drug Interaction Retrospective Study. *JCO Oncol Pract.* 2024; 20: 386-392.
93. SEER Incidence Data, November 2024 Submission. 1975-2022.
94. Cherla A, Wagner AK, Wouters OJ, Woloshin S, Davis C, Mossialos E, et al. Reporting of Clinical Trial Uncertainties With New Cancer Drugs in Journal Publications and Clinical Guidelines. *JAMA.* 2025: e2513917.