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# Long-Term Cardiovascular Mortality After Radiotherapy for Breast Cancer

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**Objectives** This study sought to investigate long-term cardiovascular mortality and its relationship to the use of radiotherapy for breast cancer.

**Background** Cardiovascular diseases are among the main long-term complications of radiotherapy, but knowledge is limited regarding long-term risks because published studies have, on average, <20 years of follow-up.

**Methods** A total of 4,456 women who survived at least 5 years after treatment of a breast cancer at the Institut Gustave Roussy between 1954 and 1984 were followed up for mortality until the end of 2003, for over 28 years on average.

**Results** A total of 421 deaths due to cardiovascular diseases were observed, of which 236 were due to cardiac disease. Women who had received radiotherapy had a 1.76-fold (95% confidence interval [CI]: 1.34 to 2.31) higher risk of dying of cardiac disease and a 1.33-fold (95% CI: 0.99 to 1.80) higher risk of dying of vascular disease than those who had not received radiotherapy. Among women who had received radiotherapy, those who had been treated for a left-sided breast cancer had a 1.56-fold (95% CI: 1.27 to 1.90) higher risk of dying of cardiac disease than those treated for a right-sided breast cancer. This relative risk increased with time since the breast cancer diagnosis ($p = 0.05$).

**Conclusions** This study confirmed that radiotherapy, as delivered until the mid-1980s, increased the long-term risk of dying of cardiovascular diseases. The long-term risk of dying of cardiac disease is a particular concern for women treated for a left-sided breast cancer with contemporary tangential breast or chest wall radiotherapy. This risk may increase with a longer follow-up, even after 20 years following radiotherapy. (J Am Coll Cardiol 2011;57:445–52) © 2011 by the American College of Cardiology Foundation



Breast cancer is becoming an increasingly survivable disease with a large population of long-term survivors due to advances in its diagnosis and treatment. The focus has therefore shifted to long-term treatment-related toxicity. Although randomized trials have demonstrated that breast irradiation significantly decreases the incidence of ipsilateral breast recurrences in women with either invasive or in situ breast cancer (1–5), long-term survivors may develop late cardiovascular toxicity due to the radiation dose delivered to the heart and the coronary arteries. During the second part of the 20th century, the radiation doses delivered to these structures were high; for example, it was estimated that breast or chest wall radiotherapy resulted in whole heart doses of 0.9 to 14.0 Gy for left-sided and of 0.4 to 6.0 Gy for right-sided irradiation. Internal mammary chain (IMC) radiotherapy delivered heart doses of 3 to 17 Gy and 2 to 10 Gy for left- and right-sided irradiation, respectively

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(6). With contemporary tangential breast or chest wall radiotherapy for a left-sided cancer, doses higher than 20 Gy are received to some parts of the heart in nearly one-half of the patients. Nevertheless, if tangential field borders are customized or advanced radiotherapy techniques are used (e.g., intensity modulated radiotherapy), heart doses are likely to be lower (7). Therefore, although radiation therapy

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**Abbreviations and Acronyms**

ICD = International Classification of Diseases

IGR = Institut Gustave Roussy

IMC = internal mammary chain

for breast cancer has long been known to induce damage in the heart (8), it is still important to investigate the magnitude of the risk of cardiovascular disease following radiotherapy for breast cancer. Indeed, although the risk of cardiac disease after radiotherapy for breast cancer has been known for about 20 years (9,10), only a small number of clinical series have a sufficiently extended follow-up to fully appreciate the magnitude of this risk.

In the present article, we report on cardiovascular mortality during the long-term follow-up of a single institution cohort of 4,456 5-year survivors of breast cancer treated between 1954 and 1984 at the Institut Gustave Roussy (IGR) and followed up for 28 years on average.

## Methods

**Materials.** THE COHORT. A cohort comprising 7,711 women initially treated at IGR for a breast cancer between 1954 and 1984 was constituted between 1984 and 1986 from IGR medical records. The study design and characteristics of the subjects were described elsewhere (11–13).The first 5 years after treatment of the initial breast cancer were excluded from the analysis (n = 2,954) because the objective was to study long-term mortality. As it was not possible to obtain the causes of death before 1972, the study mortality period was defined as extending from the beginning of 1972 to the end of 2003. An additional 301 patients were therefore excluded. Of the initial 7,711 patients, 4,456 patients fulfilled the study eligibility criteria (Fig. 1).

The following medical data were collected from the medical records: age at diagnosis, date of breast cancer diagnosis, tumor stage, tumor laterality, tumor histology, treatment, date of the last known medical status.

Patient identification data were used to obtain their vital status from the National Institute of Statistics and Economic Studies, and, if the person had died, their place of death.

The underlying causes of death were provided by the French Death Registry (INSERM [Institut National de la Santé et de la Recherche Médicale]–CepiDc [Centre d'épiémiologie sur les causes médicales de décès]) (14). Deaths were coded according to the International Classification of Diseases-Eighth Revision before 1978 (ICD-8), -Ninth Revision before 2000 (ICD-9), and -Tenth Revision thereafter (ICD-10) (14,15). We analyzed deaths separately due to cardiovascular diseases (ICD-8 [390 to 444.1, 444.3 to 458, 782.4]; ICD-9 [390 to 459, 557.0, 785.4]; ICD-10 [I00 to I99], M30, M31, R02, K55.0) and to cardiac diseases (ICD-8 and ICD-9 [390.0, 391.2, 393 to 398, 410 to 414, 420 to 429]; ICD-10 (I00 to I09, I20 to I25, I30 to I33, I39 to I52]).

TREATMENT. The period during which the disease had been diagnosed extends from 1954 to 1984. During this period, the treatments mostly consisted of radiotherapy combined with surgery or surgery alone. From 1954 to 1957, radiotherapy was delivered with a 200-kV X-ray machine (orthovoltage). From the late 1950s onward, cobalt-60 units were gradually introduced. When appropriate, the IMC was included in tangential fields. Starting in the late 1970s, the IMC in some patients was treated via a direct field with a mixed beam of Co-60 photons and electrons of the appropriate energy. The radiation dose was in general 45 Gy in 18 fractions (4 fractions per week) or 50 Gy in 25 fractions (5 fractions per week). For breast-conserving treatment, an additional booster dose of 15 Gy was usually delivered to the tumor bed. In pre-menopausal women with histologically positive lymph nodes, ovarian ablation had been performed using pelvic irradiation or surgery.

Chemotherapy was started at the IGR in the late 1970s and was mostly administered for treatment of relapses or metastases. Tamoxifen was introduced around 1975. It was first reserved for cases with a poor prognosis. Subsequently, it was used as initial or adjuvant therapy in post-menopausal women with positive estrogen receptors.

**Statistical methods.** The survival analysis was censored at 95 years of age because the quality-of-death certificates in France is lower after this age. Time at risk began 5 years after the start of the first treatment or in 1972 if earlier, and ended at the age of 95 if the person was still alive, and, otherwise, at the date of death or at the date of the last known vital status. Proportional hazard regression analysis was used for the statistical analysis. Multivariate analysis was performed to evaluate the radiotherapy effect on cardiovascular long-term mortality. This analysis was stratified on age at diagnosis (≤40, 41 to 50, 51 to 60, ≥60 years) and calendar period of diagnosis (1954 to 1957, 1958 to 1976, 1977 to 1984).

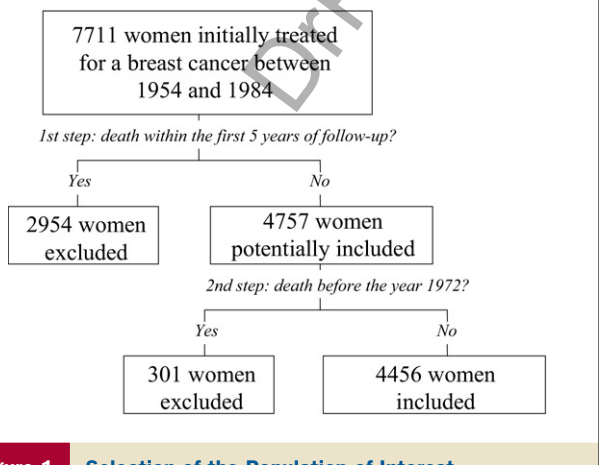


**Figure 1** Selection of the Population of Interest

Flow chart describes the selection process for this study.

## Results

Among the 4,456 women, the mean age at the time of the first treatment was 55 years (range 22 to 90 years), and the median year of the first treatment was 1976. Most of the breast cancers (81.8%) exhibited regional extension (stage II or III). Less than 1.5% were metastatic (stage IV) at the time of diagnosis. More than two-thirds of the patients had received radiotherapy as part of the primary treatment (Table 1). This treatment was associated with chemotherapy in only 268 women (6.0%). Younger patients and those treated more recently had received radiotherapy and chemotherapy more frequently. Eighty-eight percent of the women had undergone resection of lymph nodes, which were involved in 50% of the women. Eighty-nine percent of the women with lymph node involvement had received radiotherapy, as compared to 41% of those without nodal involvement. Of the 933 women who had undergone ovarian suppression, 928 had been treated with radiotherapy (Table 1).

The proportion of women with left- and right-sided breast cancers who received radiotherapy was not significantly different within many particular categories of stage, calendar year, tumor location, and age at breast cancer treatment.

Patients were followed up over a median of 28 years, representing a total of 61,662 person-years after the 5 years of minimal follow-up, and 2,637 deaths were observed before the age of 95 years. The cause of death was ascertained for 92.6% (n = 2,441) of the deaths. It was a cardiovascular disease in 421 women, including cardiac diseases in 236 and other vascular diseases in 185 (Table 2). The most frequent cardiac diseases were ischemic heart disease (n = 107), heart failure (n = 72), conduction disorders and cardiac dysrhythmias (n = 31), and the most

**Table 1** Type of Treatment According to Patient Characteristics

| | No RT, No CT | RT, No CT | CT, No RT | CT + RT |
|---|---|---|---|---|
| Overall population | 31.0 (1,381) | 62.2 (2,770) | 0.8 (37) | 6.0 (268) |
| Age at diagnosis, yrs | | | | |
| ≤40 | 24.1 (132) | 66.8 (366) | 0.9 (5) | 8.2 (45) |
| 41–50 | 26.2 (347) | 65.7 (868) | 0.8 (10) | 7.3 (96) |
| 51–60 | 32.4 (376) | 59.9 (693) | 1.1 (13) | 6.6 (77) |
| >60 | 36.8 (526) | 59.0 (843) | 0.7 (9) | 3.5 (50) |
| Period of treatment | | | | |
| 1954–1957 | 44.0 (55) | 56.0 (70) | 0 | 0 |
| 1958–1976 | 36.0 (765) | 63.8 (1,357) | 0.1 (1) | 0.1 (3) |
| 1977–1984 | 25.4 (561) | 60.9 (1,343) | 1.7 (36) | 12.0 (265) |
| Breast cancer staging | | | | |
| Stage 0–I | 29.9 (223) | 69.3 (516) | 0 | 0.8 (6) |
| Stage II and III | 31.7 (1,156) | 60.7 (2,213) | 0.9 (34) | 6.7 (243) |
| Stage IV | 3.1 (2) | 63.1 (41) | 4.6 (3) | 29.2 (19) |
| Histology of breast cancer | | | | |
| Adenocarcinoma | 30.9 (1,134) | 62.6 (2,296) | 0.9 (34) | 5.6 (203) |
| Other | 37.9 (198) | 54.2 (283) | 0.4 (2) | 7.5 (39) |
| Unknown | 18.6 (49) | 71.5 (191) | 0.4 (1) | 9.7 (26) |
| Breast cancer laterality | | | | |
| Left | 31.5 (686) | 62.0 (1351) | 1.0 (22) | 5.5 (121) |
| Right | 30.8 (625) | 61.9 (1254) | 0.7 (15) | 6.6 (134) |
| Bilateral | 25.9 (14) | 64.8 (35) | 0 | 9.3 (5) |
| Unknown | 28.7 (56) | 66.7 (130) | 0 | 4.6 (9) |
| Axillary lymph nodes | | | | |
| Not examined | 6.3 (34) | 71.6 (386) | 0.4 (2) | 21.7 (117) |
| N– (not invaded) | 59.6 (1,166) | 40.0 (782) | 0 | 0.5 (9) |
| N+ (yes invaded) | 9.2 (181) | 81.7 (1,602) | 1.8 (35) | 7.2 (142) |
| Surgery | | | | |
| No surgery | 1.7 (7) | 72.3 (300) | 0.5 (2) | 25.2 (16) |
| Breast-conserving | 0 | 96.7 (870) | 0 | 3.3 (30) |
| Total mastectomy | 47.3 (1,374) | 50.9 (1,600) | 1.1 (35) | 4.2 (132) |
| Ovarian suppression | | | | |
| No suppression | 39.1 (1,376) | 55.7 (1,959) | 1.0 (36) | 4.2 (152) |
| Suppression by RT | 0 | 86.3 (731) | 0 | 13.7 (116) |
| Suppression by surgery | 5.8 (5) | 93.0 (80) | 1.2 (1) | 0 |

Values are % (n).
CT = chemotherapy; RT = radiotherapy.

**Table 2** Deaths From Cardiovascular Disease According to Radiotherapy and the Side of the Breast Cancer

| Diseases | ICD-9 | ICD-10 | No RT | RT | RT | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Left | Right | Bilateral | Unknown Side |
| Cardiac disease | 390.0, 391.2, 393–398, 410–414, 420–429 | I00–I09, I20–I25, I30–I33, I39–I52 | 79 | 157 | 85 | 61 | 2 | 9 |
| Pericarditis | 391.0, 393, 420, 423 | I30–I32 | 0 | 0 | 0 | 0 | 0 | 0 |
| Myocarditis | 391.2, 422, 425 | I40–I43 | 5 | 1 | 1 | 0 | 0 | 0 |
| Valvular heart diseases | 390, 394–398, 421, 424 | I00–I09, I33–I39 | 1 | 12 | 6 | 3 | 0 | 3 |
| Ischemic heart diseases | 410–414 | I20–I25 | 39 | 68 | 35 | 29 | 0 | 4 |
| Conduction disorders and cardiac dysrhythmias | 426–427 | I44–I49 | 12 | 19 | 10 | 9 | 0 | 0 |
| Heart failure | 428 | I50 | 20 | 52 | 31 | 17 | 2 | 2 |
| Other heart diseases | 429 | I51-I52 | 2 | 5 | 2 | 3 | 0 | 0 |
| Pulmonary heart diseases | 415–416 | I26–I28 | 8 | 10 | 3 | 7 | 0 | 0 |
| Hypertensive diseases | 401–404 | I10–I15 | 7 | 12 | 4 | 8 | 0 | 0 |
| Vasculocerebral diseases | 430–438 | I60–I69 | 41 | 67 | 38 | 26 | 3 | 0 |
| Diseases of arteries, arterioles, and capillaries | 440–448, 557.0, 785.4 | I70–I79, K55.0, M30, M31, R02 | 15 | 16 | 10 | 6 | 0 | 0 |
| Other diseases of the circulatory system | 450–459 | I80–I89, I95–I99 | 1 | 8 | 2 | 4 | 0 | 2 |
| All | 390–459, 557.0, 785.4 | I00–I99, M30, M31, K55.0, R02 | 151 | 270 | 142 | 112 | 5 | 11 |

ICD = International Classification of Diseases; other abbreviation as in Table 1.

frequent vascular causes were vasculocerebral disease (n = 108) and diseases of arteries, arterioles, and capillaries (n = 31). During the first 30 years of follow-up after breast cancer treatment, no difference of cardiac death was observed between the women treated by radiotherapy and the women who did not receive this treatment. Considering attained-age, cardiac death risk was significantly higher among women treated by radiotherapy than for the other women (log-rank test: $p < 0.001$) (Fig. 2). In the multivariate analysis, which took into account the attained-age, cardiac mortality was 1.76-fold (95% confidence interval [CI]: 1.34 to 2.31) higher among the 3,038 women who had received radiotherapy than among those who had not, and vascular mortality was 1.33-fold (95% CI: 0.99 to 1.80), which was nonsignificantly higher (Fig. 3). In unirradiated women, breast cancer laterality was not associated with cardiac mortality ($p = 0.09$).

The risk of dying from cardiovascular disease increased with age at diagnosis ($p < 0.0001$, whatever the end point considered) (data not shown), but age at diagnosis did not significantly modify the relative risk of dying from cardiovascular disease associated with radiotherapy (p value for trend >0.2) (Fig. 3).

Among the patients who had received radiotherapy without chemotherapy and who had undergone lymph node dissection, those who had lymph node involvement or an

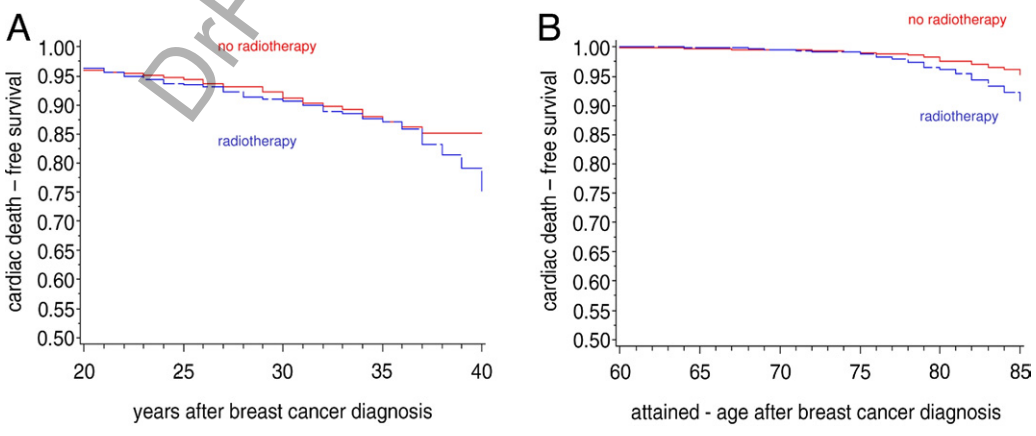


**Figure 2** Cardiac Death-Free Survival According to Radiotherapy Status

Cardiac death-free survival among women treated or not by radiotherapy according to the length of follow-up **(A)** and attained-age **(B)**.

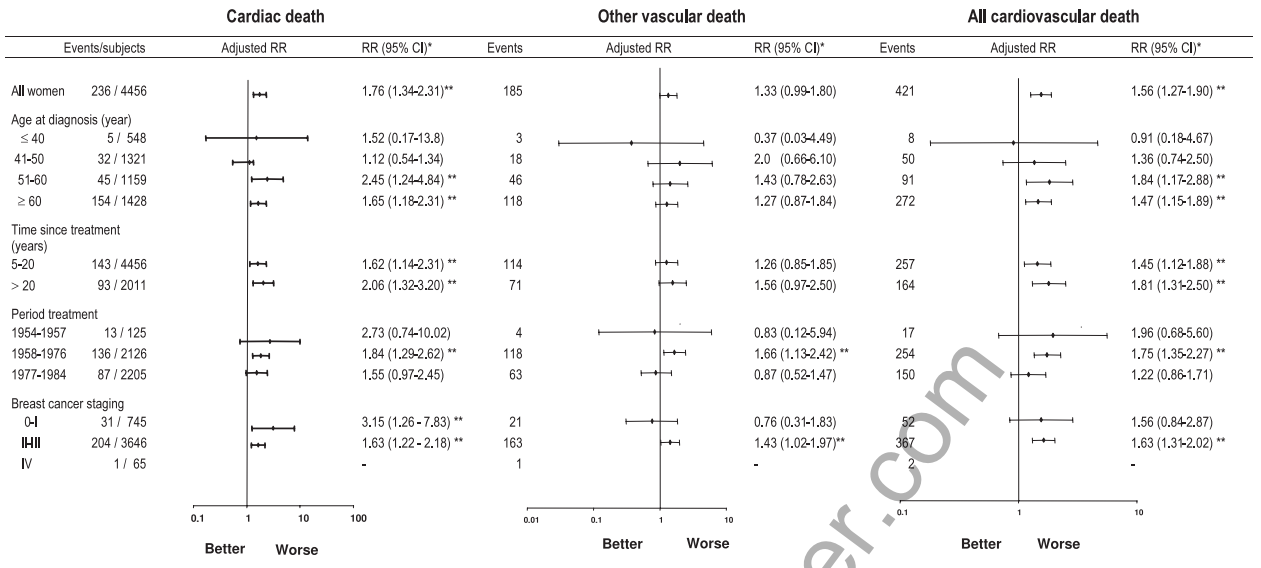


**Figure 3** **Relative Risk of Death From Cardiac, Vascular, and All Cardiovascular Diseases**

Relative risk of death from cardiac disease, vascular disease, and all cardiovascular diseases according to patient characteristics and treatments: radiotherapy versus no radiotherapy. *Multivariate analysis: the relative risk for women who had received radiotherapy as compared with the risk of women who had not, is estimated, in each category of patients, using a proportional hazard regression model adjusted for all other factors reported in the figure. **$p < 0.05$. CI = confidence interval; RR = relative risk.

internal breast cancer (called IMC group) and, therefore, had probably received irradiation to their internal mammary lymph node chain, had a 1.3-fold (95% CI: 0.8 to 2.0) higher risk of dying from cardiac disease, and a 2.1-fold (95% CI: 1.1 to 3.9) higher risk of dying from vascular disease than those who did not have nodal involvement nor internal breast cancer (called no-IMC group) and had thus received only chest wall and/or breast irradiation. When the same analysis was restricted to the 1,199 women treated for a bilateral or a left-sided breast cancer, these relative risks were, respectively, 2.0 (95% CI: 1.1 to 3.6) and 2.8 (95% CI: 1.1 to 7.2). In addition, a significant positive interaction was evidenced between the side of the breast cancer and the possible IMC irradiation ($p = 0.02$). Compared with women who had not received radiotherapy, those who had received radiotherapy for a left-sided breast cancer had a 1.77-fold (95% CI: 1.33 to 2.36) higher risk of cardiac disease, and those who had received radiotherapy for a right-sided tumor had a 1.31-fold (95% CI: 0.96 to 1.80) nonsignificantly higher risk.

After controlling for age, the period of the diagnosis, breast cancer stage, the duration of follow-up, and chemotherapy, women who had received radiotherapy for a left-sided breast cancer had a 1.28-fold higher (95% CI: 0.92 to 1.78) risk of cardiac disease than women who had received radiotherapy for a right-sided tumor. This relative risk increased with the duration of follow-up (p value for trend = 0.05), from 0.64 (95% CI: 0.29 to 1.41), from 5 to 10 years after radiotherapy, to 1.80 (95% CI: 1.01 to 3.10), for 20 years or more thereafter (Fig. 4). Similar results were obtained when we additionally controlled for ovarian ablation.

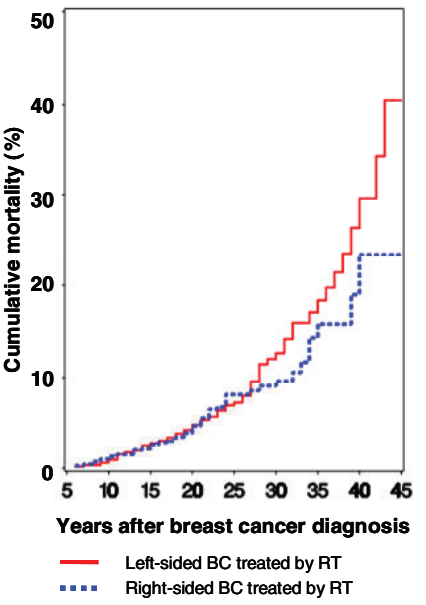


**Figure 4** **Cumulative Mortality Due to Cardiac Disease According to Breast Cancer Laterality**

Cumulative mortality due to cardiac disease according to breast cancer laterality among patients treated with radiotherapy. BC = breast cancer; RT = radiotherapy.

Of the 4,456 women, only 305 (6%) had received chemotherapy, mostly the combination of cyclophosphamide, methotrexate, and fluorouracil 5FU (or non-anthracycline-based chemotherapy). After adjusting for radiotherapy, chemotherapy was not found to have an impact on mortality due to cardiovascular diseases (relative risk [RR]: 0.70, 95% CI: 0.09 to 5.48). Similarly, the adjustment for chemotherapy did not modify the relative risks estimated for radiotherapy.

The highest relative risk associated with radiotherapy was observed for valvular diseases: of the 13 deaths due to these diseases, 12 had occurred after radiotherapy (RR: 9.01, 95% CI: 1.16 to 70) compared with those without such therapy. Elevated relative risks were also observed for ischemic heart disease (68 deaths after radiotherapy: RR: 1.52, 95% CI: 1.02 to 2.26) and heart failure (52 deaths after radiotherapy, RR: 2.39, 95% CI: 1.41 to 4.03).

## Discussion

We followed up 4,456 5-year survivors of breast cancer treated at IGR from 1954 to 1984, for over 28 years on average. Five-year survivors who had received radiotherapy during their breast cancer primary treatment were at a higher risk of death from overall cardiovascular diseases, and cardiac diseases, as compared to women who had not received radiotherapy. Women who had received radiotherapy for a left-sided breast cancer were at a higher risk of cardiac death than those who had received it for a right-sided tumor, and this difference increased with the duration of follow-up.

As with any hospital-based study, our analysis is subject to some biases. However, these limitations are counterbalanced by the advantages of having a large hospital-based cohort with a very long-term follow-up and standardized treatment protocols. In our study, selection bias is certainly limited, as IGR has kept all medical records since its creation in 1944, allowing exhaustive data collection. Moreover, our cohort was established from 1984 to 1986, and then most of the information on mortality analyzed in this report occurred during the prospective follow-up, after collecting data concerning the initial treatment. Nevertheless, only randomized trials on adjuvant radiotherapy are theoretically able to measure, devoid of biases, the iatrogenic effects of radiations among women treated for a breast cancer. Outside trials, patients may have been selected for irradiation not only according to their age and the nature of their breast cancer, but also according to factors that are correlated with their prognosis. Therefore, simple comparisons of the subsequent mortality of irradiated and unirradiated patients cannot be used to assess reliably the real benefit and hazards of treatment. In our study, the proportion of women with left- and right-sided breast cancers who received radiotherapy was not significantly different within many particular categories of stage, calendar year, tumor location, and age at breast cancer treatment. This suggests that breast cancer laterality played little part in determining who should be given radiotherapy. Also, in unirradiated women, breast cancer laterality was not associated with cardiac mortality ($p = 0.09$). Hence, the relevance of breast cancer laterality in irradiated women to subsequent mortality from heart disease can be used to help to assess the long-term hazards of radiotherapy regiments actually given.

As our aim was to study the potential long-term iatrogenic risk of radiotherapy rather than to assess its overall efficacy, we excluded 2,954 women who had died during the first 5 years after the first treatment for breast cancer, as these cases were therefore considered uninformative for the main end points.

In our study, the causes of death for women from the cohort were extracted from the CepiDc database, which is a national registry of causes of death. To compare our data with data from other cohorts, we used only causes of death that were classified as the "main" cause of death and did not use information on the cause of death registered in the medical records. This was done to avoid potential sources of biases. Nevertheless, the accuracy of cause-of-death coding could be a source of concern for patients who survive a cancer. When we compared the causes registered in the IGR medical records and those obtained from the CepiDc, which was possible for 2,353 deaths, 79% of the deaths classified as due to breast cancer in the medical records were also classified as death from breast cancer by the CepiDc, the inverse proportion being 80%.

When we interpreted our findings concerning the role of radiotherapy in long-term mortality, we hypothesized that genetic and lifestyle factors, which influence the severity of the disease, or any other determinants of treatment decisions do not play an independent role in long-term mortality due to cardiovascular diseases. Such factors do, however, play a role in the risk of cardiovascular diseases. We were unable to correct for this potential source of bias, which can ideally be controlled in randomized clinical trials (1).

Our study confirms excess mortality due to cardiac diseases in women treated with radiotherapy for a breast cancer, as compared with women who were not. This result is consistent with many randomized (1,10,16,17) and observational studies (18–20) and systematic reviews (3,21,22). In our cohort, the excess risk of death due to radiotherapy was 56% and 76% for all cardiovascular diseases and cardiac diseases, respectively. These values are in agreement with that observed in other studies, most of which evidenced higher cardiac mortality following radiotherapy for a left-sided breast cancer than for a right-sided lesion (10,19,20,23–27). Nevertheless, some studies did not observe such excess mortality (18,28–31). In another study, no overall excess cardiac mortality was observed, but there was an increased incidence of coronary artery disease and myocardial infarction (32). In our study, the relative risk of cardiac mortality following radiotherapy for a left-sided tumor versus a right-sided tumor was 1.28 (95% CI: 0.92 to 1.78) and increased with increasing follow-up. Our overall

estimation is consistent with a relative risk of 1.2 (95% CI: 1.1 to 1.2) estimated by Darby et al. (19) based on the SEER (Surveillance, Epidemiology, and End Results) data of the U.S. National Cancer Institute, that of 1.1 (95% CI: 1.0 to 1.2) obtained for long-term deaths (>10 years) in the Swedish cohort study (20), and that of other reports (1.36 in Haybittle et al. [10], 1.17 in Paszat et al. [24], 1.16 in Paszat et al. [25]). In a study limited to myocardial infarction (23), a relative risk of death of 2.10 (95% CI: 1.11 to 3.95) was evidenced for radiotherapy delivered to the left side. The strong increase in risk that we observed after 20 years of follow-up is consistent with the fact that the risk increased with follow-up in most of the studies (1,20,32,33).

In our cohort, among the cardiac diseases, the highest risk associated with radiotherapy was observed for death from valvular heart disease (RR: 9.01, 95% CI: 1.16 to 70). In the Netherlands Cancer Institute cohort (34), a high risk of these diseases was observed in women who had received radiotherapy to the IMC (hazard ratio: 3.17, 95% CI: 1.90 to 5.29).

Our study also shows that women treated for a right-sided breast cancer are also at a nonsignificantly higher risk of mortality due to cardiac diseases than those who had not received radiotherapy. Based on current knowledge, this excess risk, if confirmed, is unlikely to be attributable to low doses (<1 Gy) of radiation to the heart delivered during radiotherapy limited to the right breast, but rather to radiotherapy delivered to the IMC for right-sided breast cancer during which part of the heart is included in the radiotherapy fields. Indeed, to date, apart from the notable exception of a study on U.S. nuclear workers (35), there is no compelling evidence of an increase in cardiovascular diseases for radiation doses below 5 Gy (36,37); in other words, the average heart dose that is not usually reached during radiotherapy is limited to the right breast. In addition, in our study, a significant positive interaction was evidenced between the side of the breast cancer and the possible IMC irradiation ($p = 0.02$).

Very few women received chemotherapy in this cohort. Therefore, we were not able to investigate in detail the impact of this treatment on cardiovascular mortality. Similarly, we were not able to investigate the role of hormonal suppression because all women who had received hormonal therapy had also received radiotherapy (Table 1).

## Conclusions

Our results confirm that radiotherapy for breast cancer, such as that practiced until the mid-1980s, increased the long-term risk of death from cardiac disease. The excess mortality due to cardiac disease was significantly higher following radiotherapy for left-sided than for right-sided breast cancer. Our cohort is the first to show that this difference increases with increasing follow-up, even after 25 years of follow-up.

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**Key Words:** breast cancer ■ cardiac disease ■ cardiovascular diseases ■ causes of death ■ long-term mortality ■ long-term risk ■ radiotherapy.