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Long-term risk of heart failure in breast cancer patients after adjuvant chemotherapy with or without trastuzumab.

Short title: Long term risk of heart failure after trastuzumab

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‡‡Senior authors Morten Schou and Jacob E. Møller contributed equally.

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Abstract:

Objective
The aim of this study was to evaluate the risk of developing heart failure (HF) on long-term after trastuzumab treatment.

Background
Trastuzumab has improved the prognosis in HER2 positive breast cancer, but can induce left ventricular dysfunction with reduced ejection fraction or HF during treatment. The long-term risk of HF is less well described.

Methods
In a nationwide, retrospective cohort study 9,901 patients scheduled for adjuvant treatment for early-stage breast cancer, were identified in Danish Breast Cancer Cooperative Group database. Of these 8,812 patients (25% HER2 positive, age: 51.7±8.5) received chemotherapy including anthracycline and if HER2 positive trastuzumab was added. The primary endpoint was a diagnosis of HF assessed before and after 18 months in a landmark analysis to distinguish short and long-term risk.

Results
Median follow-up was 5.4 years (IQR: 4.1-6.8). In the trastuzumab group 60 patients had HF by nine years vs. 51 in the group treated with chemotherapy alone corresponding to incidence rates per 1000 patient years of 5.3 (95% CI: 4.1-6.8) vs. 1.4 (95% CI: 1.1-1.8). The cumulative incidence of HF was higher in the trastuzumab group on both short and long-term (p<0.01), yielding adjusted hazard ratios of 8.7 (95% CI: 4.6-16.5, p<0.01) for early HF and of 1.9 (95% CI: 1.2-3.3, p=0.01) for late HF associated with trastuzumab treatment.

Conclusion
Trastuzumab treatment is associated with a two-fold increased risk of late HF compared with chemotherapy alone.

Key words: Heart failure, Carditoxicity, Breast Cancer, Trastuzumab, Epidemiology
Abbreviation list:

DBCG = the Danish Breast Cancer Cooperative Group
HER2 = Human Epidermal Growth Factor Receptor 2
HERA = Herceptin Adjuvant Trial
HF = heart failure
ICD-10 = the 10th revision of the International Classification of Diseases
LVEF = Left ventricular ejection fraction
MUGA = Isotope Multi Gated Acquisition scan
Introduction

Breast cancer is the most frequent malignant disease among women worldwide with estimated 1.67 million new cases diagnosed in 2012, corresponding to 25% of all cancers in women (1). About 15-30% of breast cancer patients have a subtype of cancer with expression of the Human Epidermal Growth Factor Receptor 2 (HER2), which is associated with accelerated tumor growth, early metastasis, and thus a poor prognosis (2-4). Trastuzumab, a humanized monoclonal antibody directed against HER2, has significantly improved survival in HER2 positive breast cancer patients, but can induce asymptomatic left ventricular dysfunction with reduced ejection fraction or symptomatic heart failure (HF) (5-7).

Randomized trials testing trastuzumab in an adjuvant setting have reported a 5-fold increased risk of cardiac toxicity with development of symptomatic HF in 1-2 % of the patients within the first two years after treatment initiation (8). There is more uncertainty about the long-term risk, with evidence from clinical trials revealing no excess risk of HF after the first two to three years (9-11), whereas some observational studies of clinical populations suggest, that the incidence might be higher up to 20 % and the duration of the risk period longer (12,13). With a current 5-year survival of more than 85% after a diagnosis of breast cancer in developed countries, long-term cardiac adverse effects of therapy become important (14), especially since cardio-vascular comorbidity is proposed to be a major contributor to overall long-time survival (15).

After randomization in the Herceptin Adjuvant Trial (HERA) (16), trastuzumab was introduced in 2006 as a guideline treatment in Denmark recommended by the Danish Breast Cancer Cooperative Group (DBCG). This nationwide multidisciplinary group with an associated database was established in 1977 with the aim to improve the prognosis in breast cancer (17). With this unique
source of data, we were able to evaluate the long-term risk of clinical HF after adjuvant chemotherapy with and without trastuzumab in an entire population of unselected women with early stage breast cancer.

**Methods**

**Design**

This is a nationwide, retrospective cohort study based on data linked on an individual level between the complete Danish administrative and clinical registries by the unique civil registration number, which is provided to all Danish citizens at birth or at achievement of permanent residency in Denmark (18).

**Data sources**

The primary study endpoint was a diagnosis of HF in the Danish National Patient Registry defined by the following International Classification Diseases (ICD)-10 codes: DI50-50.9, DI42-42.9, DI11.0, DI13.0 and DI13.2. The diagnosis of heart failure mainly comprises systolic HF (19). The Danish National Patient Registry holds nationwide data on ICD codes on all hospital admissions since 1977, and since 1995 data on outpatient and emergency patients (20). Diagnoses based on only emergency visits or in outpatients seen on one occasion with no further follow-up of chronic HF were not counted as an event. The diagnosis of HF in the Danish National Patient Registry has been validated at several occasions with positive predictive values between 81 and 100% (19,21). Vital status was recorded from the Danish Civil Registry (18) and causes of death from The Danish Register of Causes of Death (20).
Covariate data regarding tumor characteristics and cancer treatment were collected from the DBCG database, which contains information on Danish women diagnosed with breast cancer since 1977 (17). Data on cardiovascular co-morbidity were obtained from the Danish National Patient Registry.

Study cohort

Consecutive patients with surgery for unilateral non-metastatic breast cancer between the 1\textsuperscript{st} of January 2007 and the 31\textsuperscript{th} of December 2012 were identified in DBCG database. Patients allocated to chemotherapy and if HER2 positive also to trastuzumab, but no other biological treatment, were included. Patients were excluded if they did not receive chemotherapy or trastuzumab, were aged ≥70 years, or had a diagnosis of HF prior to the diagnosis of breast cancer. The adjuvant chemotherapy consisted of three cycles of epirubicin (90 mg/m\textsuperscript{2}) and cyclophosphamide (600 mg/m\textsuperscript{2}) followed by three cycles of docetaxel (100 mg/m2), and if HER2 positive one year of trastuzumab distributed on 17 individual cycles. 987 patients (108 HER2 positive and 879 HER2 negative) included in this cohort were randomized to a different chemotherapy regime consisting of six cycles of docetaxel (75 mg/m2) and cyclophosphamide (600 mg/m2) (22). If indicated by guidelines patients also received radiation and endocrine therapy (23,24). During trastuzumab therapy patients had repeated isotope Multi Gated Acquisition (MUGA) scans evaluating left ventricular ejection fraction (LVEF) at weeks 0, 9, 18, 30 and 48 after initiating trastuzumab according to DBCG guidelines. Patients receiving chemotherapy alone did not have any routine cardiac evaluations.

Patients were followed from the date of surgery and to the first occurrence of the primary endpoint, a competing event of death, a censoring event of emigration, or end of study follow-up period (the 31\textsuperscript{th} of December, 2015).
Statistics

Baseline characteristics were described using proportions for categorical variables and median and interquartile range for continuous variables. The Wilcoxon two-sample test and the Chi-Square test were used for comparison of baseline characteristics.

A landmark time point was set at 18 months. Landmark analyses of HF risk were used to assess incidence of HF before and after 18 month from index to distinguish between short and long-term risk. Hence, those patients followed after 18 months had not died or received a diagnosis of HF from index to 18 months.

Incidence rates per 1000 patient years for HF were calculated. Due to competing risk of death, the incidence of HF was evaluated in a cumulative incidence function with death as a competing endpoint and Grey’s test for equality was applied to examine differences between groups. An additional analysis of cumulative incidence of HF stratified according to age was conducted. Kaplan-Meier estimates based on all-cause mortality were calculated and the Log-Rank test applied.

Risk of HF was examined multivariate in a cause-specific Cox Proportional Hazard Model adjusted for age and baseline comorbidity (ischemic heart disease, acute myocardial infarction, atrial fibrillation, hypertension, type 2 diabetes mellitus and chronic obstructive pulmonary disease) with the Wald Chi-Squared test applied. When the proportional hazards assumption was assessed graphically by a log(-log) S plot and by adding a time-dependent variable to the model for the early and late HF assumptions of proportional hazards were met.

For purposes of sensitivity analyses, we modeled the propensity for receiving trastuzumab treatment versus not, using all available baseline characteristics (see table 1 and 2) (logistic regression analysis with trastuzumab treatment as outcome variable). The propensity score yielded by this
model was divided into quintiles and the cause-specific hazard model was performed again with model stratification for propensity, i.e. cases and controls were only compared within strata of propensity scores.

The SAS statistical software package, version 9.4. (SAS Institute, Gary, NC) was used for statistical analysis and data management. A two-sided P-value <0.05 was considered statistical significant.

**Ethics**

The study was approved by the Danish Data Protection Agency (Ref. No. 2007-58-0015/GEH-2014-012; I-Suite No. 02720). Approval by the Ethics Committee and informed consent are not required for retrospective register based studies in Denmark.

**Results**

**The study cohort**

From the DBCG database 9,901 patients scheduled for adjuvant medical treatment after surgery for unilateral non-metastatic breast cancer were identified. Of these 1,089 patients were excluded from the analysis due to no receipt of treatment (n = 288), age ≥70 years (n = 753) or a pre-existing diagnosis of HF before the diagnosis of breast cancer (n = 48). Of the remaining 8,812 patients, 2,117 had HER2 positive disease and received both chemotherapy and trastuzumab treatment, whereas 6,695 patients were HER2 negative and received solely chemotherapy as part of the adjuvant medical treatment. Details are presented in the consort diagram, figure 1.

As presented in table 1, patients in the chemotherapy + trastuzumab treatment group were on average slightly older than patients in the solely chemotherapy group with a mean age of 53.5 (SD ± 9.6) years vs 51.2 (SD ± 8.1). Differences in tumor characteristics and other treatment modalities
between the chemotherapy + trastuzumab and the chemotherapy group are also presented in table I. Median accumulated dose of trastuzumab was 6761 mg (IQR: 5700-7800) among the chemotherapy + trastuzumab treated patients.

Table 2 demonstrates a low prevalence of comorbidity in the cohort at baseline, which was balanced between groups.

The cohort used for the analysis of late HF consisted of 8,611 patients, who survived and did not develop HF within the first 18 months after initiation of trastuzumab (consort diagram presented in supplementary, figure 1a). Baseline characteristics and comorbidity for the cohort used for analysis of late HF are presented in supplementary, table 3 and 4. Comorbidity was up-dated to 18 month.

Follow-up was complete with a median follow-up period of 5.4 years (IQR: 4.1-6.8). Mortality was similar in both groups: 14.5% (95% CI: 12.4-17.0) in the chemotherapy + trastuzumab group vs. 15.3% (95% CI: 13.4-17.2) in the chemotherapy alone group (p=0.67). Cause of death was primarily cancer with no difference (86.7% vs. 89.6%, p=0.27) between the two groups respectively. Cardiovascular death constituted 3.3 % vs. 2.7 % with no difference between groups (p=0.70). Divided according to the landmark analysis before and after 18 month, mortality was also similar between the two treatment groups with 1.2% (95% CI: 0.9-1.8) vs. 1.9% (95% CI: 1.6-2.2) (p=0.06) from 0 – 18 months and 13.3% (95% CI: 11.1-15.7) vs. 13.6% (95% CI: 11.7-15.6) (p=0.24) after 18 months. There was no difference between the groups regarding cancer and cardiovascular mortality before and after 18 months.

Incidence and risk of heart failure

In the chemotherapy + trastuzumab treatment group 60 new cases of HF (2.8%) were identified vs. 51 (0.8%) in the group treated with chemotherapy alone, corresponding to incidence rates per 1000
patient years of 5.3 (95% CI: 4.1-6.8) vs. 1.4 (95% CI: 1.1-1.8). In the chemotherapy +
trastuzumab group 41.7 % were diagnosed in relation to a hospital admission as oppose to in an
outpatient clinic, whereas 76.5% (p<0.001) were diagnose during an admission in the chemotherapy
alone group.

The landmark analysis of patients diagnosed with HF within the first 18 months after the diagnosis
of breast cancer revealed 36 cases (1.7%) of early HF in the chemotherapy + trastuzumab group vs.
13 (0.2%) in the chemotherapy alone group, corresponding to incidence rates per 1000 patient years
of 11.8 (95% CI: 8.5-16.3) vs. 1.3 (95% CI: 0.8-2.3), whereas analysis after 18 months
demonstrated 24 cases (1.2%) of late HF in the chemotherapy + trastuzumab treatment group vs. 38
(0.6%), corresponding to incidence rates per 1000 patient years of  2.9 (95% CI: 1.9-4.3) vs. 1.4
(95% CI: 1.0-1.9).

The cumulative incidence of HF after 9 years, including all cases of HF, was 3.3% (95% CI: 2.5-
4.2) in the chemotherapy + trastuzumab group vs. 1.3% (95% CI: 0.9-1.8) (p<0.0001). Development of both early and late HF was significantly increased among patients treated with
chemotherapy + trastuzumab compared with chemotherapy alone as presented in the landmark
analysis, figure 2.

Increased cumulative incidence in the group treated with both chemotherapy and trastuzumab
compared to chemotherapy alone stratified according to age is presented for early HF (p<0.0001),
figure 3a and for late HF (p=0.03), figure 3b.

Including all cases of HF in the Cox Proportional Hazard model, an age and comorbidity adjusted
hazard ratio (HR) of 3.61 (95% CI: 2.47–5.26, p<0.0001) was found for HF associated with
chemotherapy + trastuzumab treatment relative to chemotherapy alone. In the landmark analysis
including only cases of early HF, the adjusted HR associated with trastuzumab was 8.69 (95% CI:
4.59–16.47, p<0.0001) and for cases of late HF was 1.93 (95% CI: 1.15–3.25, p=0.01). In the multivariate analysis, ischemic heart disease, acute myocardial infarction, and chronic obstructive pulmonary disease were associated with development of early HF, whereas ischemic heart disease, atrial fibrillation, and type 2 diabetes were associated with development of late HF. The estimates are illustrated in supplementary figure 4.

In a sensitivity analysis, a propensity score based on all baseline variables was added to the model without any major change in the HRs associated with trastuzumab, which in this analysis were of 3.87 (95% CI: 2.61–5.74, p<0.0001) for all cases, 10.19 (95% CI: 5.27–19.70, p<0.0001) for early cases and 1.90 (95% CI: 1.10–3.26, p=0.02) for late cases.

Discussion

This nationwide cohort study evaluated the long-term risk of clinical HF after chemotherapy and trastuzumab treatment compared to chemotherapy alone in an unselected cohort of unilateral early-stage breast cancer patients. The main finding was an increased long-term risk of HF after chemotherapy and trastuzumab treatment compared with chemotherapy alone, but with an overall low incidence. The risk of HF was weakly associated with baseline comorbidity. Finally, the study confirmed the early risk of HF associated with trastuzumab during treatment.

Incidence and risk of heart failure

The increased incidence of late HF observed in the present study differs from data recently published on cardiac side effects from some of the first randomized trials testing trastuzumab treatment in an adjuvant setting with up to eight years of follow-up. Both the HERA and NSABP (B-31) trial reported an increased risk of HF during and shortly after trastuzumab treatment, but
with very few cases of suspected cardiac toxicity on long-term follow-up (9,11). This difference is likely explained by the favorable cardiovascular risk profile of women in the randomized trials compared with a clinical population with a presumably greater burden of comorbidity. Interestingly, Goldhar et al. recently conducted a population-based study of Canadian breast cancer patients and found a similar result as the randomized studies, with a HR of 5.77 of developing HF within the first 18 months, but thereafter no excess risk of HF could be detected. Although the Canadian cohort share similar age and prevalence of myocardial infarction with our cohort, diabetes and hypertension were more prevalent in the Canadian cohort, therefore, comorbidity is unlikely to explain the difference alone (25). Other observational studies report increased risk of HF compared to the randomized trials, especially among elderly patients, but follow-up duration was shorter and there was no differentiation between early and late HF development (13, 26).

In the present study, the cumulative incidence of just below 3% of patients developing HF during the first five years of follow-up is comparable with the large Canadian observational study with approximately 5% (25) and the NSABP (B-31) trial with below 4% (27). In the HERA study the cumulative incidence was even lower with approximately 1% (11). These low incidences are as mentioned earlier likely explained by a lower cardiovascular risk profile in the randomized trials, but might also suggest that patients referred to chemotherapy in a clinical setting could in some degree be selected. It has previously been suggested in a large epidemiological study, that breast cancer patients have a favorable cardiovascular risk profile compared with the background population (28). However, a recent nationwide register study on the general incidence of HF in the Danish background population, found incidence rates of 6.4 and 17 per 10,000 person years among individuals between 45-54 and 55-64 years, which is lower than the findings in the present study (29). Incidences of HF among women in the Framingham and the Hillingdon Heart studies are also
below our results, even though direct comparison is difficult due to differences in age and methods (30).

**Age and comorbidity**

The cumulative incidences stratified according to age in our study indicate, with reservation for the low number of cases in each group, that early HF development during trastuzumab treatment is less associated with age, than in patients developing late HF. It has previously been shown, that the risk of HF associated with trastuzumab is higher among elderly patients, but without the differentiation between early and late HF (13). The association with cardiovascular comorbidity, which has also been described in other studies (13,25), was also present in this study. Further, the isolated association with age in this study was erased when comorbidity was added to the multivariate model.

**Clinical implications**

With many long term survivors after modern breast cancer treatment, (14) awareness of HF as a possible long term consequence of trastuzumab treatment is important. Even though the overall risk of HF after trastuzumab treatment is low, it might be relevant to take this risk into consideration, when planning the course of follow-up after HER2 positive breast cancer, especially in patients with other comorbidities as this seems associated with a later diagnosis of HF. When a patient is diagnosed with HF or symptoms of this, it is of importance to gain detailed information about previous cancer treatment, when determining the etiology, and keeping in mind that trastuzumab even several years after treatment could be a contributing factor.
Strengths and limitations

Given the observational design of the study, the results should be interpreted with caution. However, to the best of our knowledge, there are very few studies on clinical populations with comparable size in terms of number of patients treated with trastuzumab. The complete follow-up in this study is also a strength as is the quality of Danish nationwide registries, where the completion of the registries is ensured by an obligation by legislation to report to these registries (20). Further, the certainty of the HF diagnosis in the Danish National Patient Registry is reasonable high with positive predictive values between 81 and 100% in validation studies (19,21). A limitation of the National Patient Registry is, however, that only patients, who presents with symptoms severe enough to require an outpatient hospital visit or hospitalization are recorded. The incidence is likely underestimated, since a number of patients with early stages of HF, asymptomatic patients with reduced ejection fraction or very limited symptoms are not diagnosed and consequently not recorded in the Danish National Patient Registry.

There was a difference in age between the two treatment groups in this study with patients treated solely with chemotherapy being slightly younger the patients treated with both chemotherapy and trastuzumab, since HER2 negative patients above 60 years of age according to treatment guidelines only were scheduled for adjuvant medical treatment, if specific tumor characteristics placed them in high risk for recurrence. The risk analysis was, however, adjusted for age, and the sensitivity analysis with addition of propensity score did not change the risk estimate.

We may have overestimated the effect of trastuzumab on the risk of heart failure, as part of the risk may be explained by different exposure to antracyclin between the two groups, since we lack exact information on doses. However, 96 % of the patients in the trastuzumab treatment group received an antracyklin and 88 % in the group treated with both chemotherapy and trastuzumab.
Therefore, a sensitivity analysis was conducted with exclusion of the number of patients, who did not receive an anthracycline. This analysis did not change the risk estimate.

Since the risk of early HF during trastuzumab treatment is well known, patients in the group treated with both chemotherapy and trastuzumab might have more attentions towards HF symptoms and some degree of observational bias cannot be excluded in relation to late HF. This assumption is supported by the larger proportion of patients diagnosed in an outpatient clinic (presumably with less critical symptoms) in the chemotherapy + trastuzumab group as opposed to a larger proportion diagnosed during a hospital admission in the chemotherapy group.

**Conclusion**

In this nationwide cohort study based on real-life data trastuzumab treatment after anthracycline-based chemotherapy was associated with a two-fold increased risk of late clinical HF compared to anthracycline-based chemotherapy alone and associated with baseline cardiovascular comorbidity. This increased risk should be taken into account when planning the course of follow-up after cancer treatment and should be kept in mind, when determining the etiology of HF or cardiomyopathy in long term cancer survivors.

**Clinical perspectives**

COMPETENCY IN MEDICAL KNOWLEDGE: With many long-term cancer survivors the finding of increased long-term risk of HF after trastuzumab treatment should be kept in mind when patients present with HF many years after a diagnosis of cancer. Further, previous use of trastuzumab should be kept in mind when the etiology of the cardiomyopathy is determined.
TRANSLATIONAL OUTLOOK: The risk of cardiotoxicity during trastuzumanb treatment is well known, but the present study finds indications of comorbidity being more a contributing factor in long-term than in short-term risk of heart failure in relation to trastuzumab. Further research is needed to establish the significance of this.

Acknowledgements

A great acknowledgment to the Danish Breast Cancer Cooperative Group for access to the breast cancer database.
References:


Figure Legends (title and caption):

Figure 1: Consort diagram.
Consort diagram illustrating the study population.

Figure 2: Landmark analysis of heart failure.
Cumulative incidence of HF in patients treated with chemotherapy +/- trastuzumab before (p<0.0001) and after 18 month after the diagnosis of breast cancer (p<0.01).

Figure 3: Heart failure according to age.
a). Cumulative incidence of early HF stratified according to age in patients treated with chemotherapy +/- trastuzumab for breast cancer (p<0.0001). b). Cumulative incidence of late HF stratified according to age in patients treated with chemotherapy +/- trastuzumab for breast cancer (p=0.03). Braces are representing 95% CI.
Figure 1: Consort diagram.

Unilateral non metastatic breast cancer patients
1/1-2007 – 31/12 - 2012
n =9901

HER2 positive
n = 2561
- No treatment
  n = 62
- Age ≥70
  n = 370
- Pre HF
  n = 12

HER2 negative
n = 7340
- No treatment
  n = 226
- Age ≥70
  n = 383
- Pre HF
  n = 36

HER2 positive in analysis = chemotherapy + trastuzumab
n = 2117

HER2 negative in analysis = chemotherapy
n = 6695
Figure 2: Landmark analysis of heart failure.
Figure 3: Heart failure according to age.
<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Chemotherapy + trastuzumab (n = 2117)</th>
<th>Chemotherapy (n = 6695)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Mean age:</td>
<td>53.5 (SD ± 9.6)</td>
<td>51.2 (SD ± 8.1)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>≤ 39 years</td>
<td>9.6% (203)</td>
<td>9.5% (636)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>40 – 49 years</td>
<td>24.5% (518)</td>
<td>31.7% (2125)</td>
<td></td>
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<tr>
<td>50 – 59 years</td>
<td>38.7% (819)</td>
<td>49.5% (3313)</td>
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<tr>
<td>60 - 70 years</td>
<td>27.3% (577)</td>
<td>9.3% (621)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal status</td>
<td>57.6% (1220)</td>
<td>48.5% (3221)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Breast cancer therapy:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breast conserving surgery</td>
<td>53.5% (1132)</td>
<td>65.2% (4367)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Radiotherapy</td>
<td>74.5% (1577)</td>
<td>82.9% (5553)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Neoadjuvant therapy</td>
<td>8.4% (178)</td>
<td>4.3% (286)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Tumor characteristics:</td>
<td></td>
<td></td>
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<tr>
<td>Involvement of lymph nodes</td>
<td>49.2% (1041)</td>
<td>54.9% (3678)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Positive estrogen receptor status</td>
<td>60.8% (1288)</td>
<td>75.0% (5019)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Size:</td>
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<tr>
<td>0 - 20 mm</td>
<td>54.3% (1150)</td>
<td>55.3% (3704)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Size</td>
<td>21 – 50 mm</td>
<td>&gt;50 mm</td>
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<td>-----------</td>
<td>---------</td>
<td></td>
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<tr>
<td></td>
<td>33.8% (715)</td>
<td>37.2% (2487)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.9% (61)</td>
<td>2.9% (196)</td>
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**Histologic type:**

<table>
<thead>
<tr>
<th>Type</th>
<th>Patients</th>
<th>Controls</th>
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<tr>
<td>Ductal</td>
<td>92.7% (1963)</td>
<td>83.8% (5607)</td>
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<tr>
<td>Lobular</td>
<td>1.8% (39)</td>
<td>8.2% (549)</td>
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<tr>
<td>Other</td>
<td>5.4% (115)</td>
<td>8.0% (539)</td>
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**Malignancy grade:**

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<th>Grade</th>
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<th>Controls</th>
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<tbody>
<tr>
<td>I</td>
<td>5.6% (119)</td>
<td>17.9% (1201)</td>
</tr>
<tr>
<td>II</td>
<td>35.6% (754)</td>
<td>44.3% (2967)</td>
</tr>
<tr>
<td>III</td>
<td>47.2% (1000)</td>
<td>28.4% (1901)</td>
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Table 2. Baseline comorbidity

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Chemotherapy + trastuzumab n = 2117 % (n)</th>
<th>Chemotherapy n = 6695 % (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>3.1% (66)</td>
<td>2.5% (168)</td>
<td>0.13</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0.6% (12)</td>
<td>0.5% (32)</td>
<td>0.61</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.9% (20)</td>
<td>0.6% (39)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.5% (179)</td>
<td>7.4% (493)</td>
<td>0.10</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>2.5% (53)</td>
<td>2.1% (139)</td>
<td>0.24</td>
</tr>
<tr>
<td>COPD*</td>
<td>1.6% (34)</td>
<td>1.4% (91)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Chronic obstructive pulmonary disease