

Supplementary material

Inclusion and exclusion criteria for the DBCG 89 TM program were:

Inclusion:

- Primary invasive breast cancer
- Age <70 years
- A good cosmetic result is obtainable
- 10 mm macroscopic and 5 mm microscopic resection margin is achievable
- The patient accepts post-operative radiation therapy

Exclusion:

- Metastatic disease at the time of diagnosis
- Bilateral breast cancer
- Previous breast cancer
- Inflammatory breast cancer and Paget's disease of the nipple
- Prior malignant disease apart from non-melanoma skin tumors or in situ cervix cancer

Assessment of histological type and grade:

The WHO classification was used to define the tumor histological type [24], and the method of Bloom and Richardson, modified by Elston and Ellis [25], was used for assessing tumor grade.

Assessment of estrogen receptor status:

A tumor was considered to be ER-positive if at least 10% of the invasive tumor cells showed a detectable nuclear staining [26].

Definition of menopausal status according to the DBCG:

Patients were premenopausal if they did not meet the criteria for being post-menopausal (see below).

Patients were postmenopausal if they had menostasia for 12 or more months, or had prior bilateral oophorectomy, or prior hysterectomy, or menstruation on cyclic hormonal therapy and were 50 years or

more. Patients with menostasia for 2-12 months were examined with blood test measuring FSH level to determine menopausal status.

Details on the administration of adjuvant systemic treatment:

Group A received no adjuvant systemic treatment.

Group B received CMF-chemotherapy (Cyclophosphamide, Methotrexate, 5-Fluorouracil), 9 cycles given intravenously on day one, every third week, or ovarian ablation either by surgery or irradiation. From 1998 onwards a third treatment arm containing chemotherapy CEF (Cyclophosphamide, Epirubicin, 5-Fluorouracil) 9 cycles given intravenously on day one, every third week + Tamoxifen for 5 years was introduced in this group. CMF was given in doses of 600/40/600 mg/m², and CEF in doses of 600/60/600 mg/m²

Group C received Tamoxifen for 1 or 2 years, or Tamoxifen for ½ year followed by Megestrol for ½ year.

Group D received CMF, CMF + Pamidronate, CEF, or CEF + Pamidronate [1].

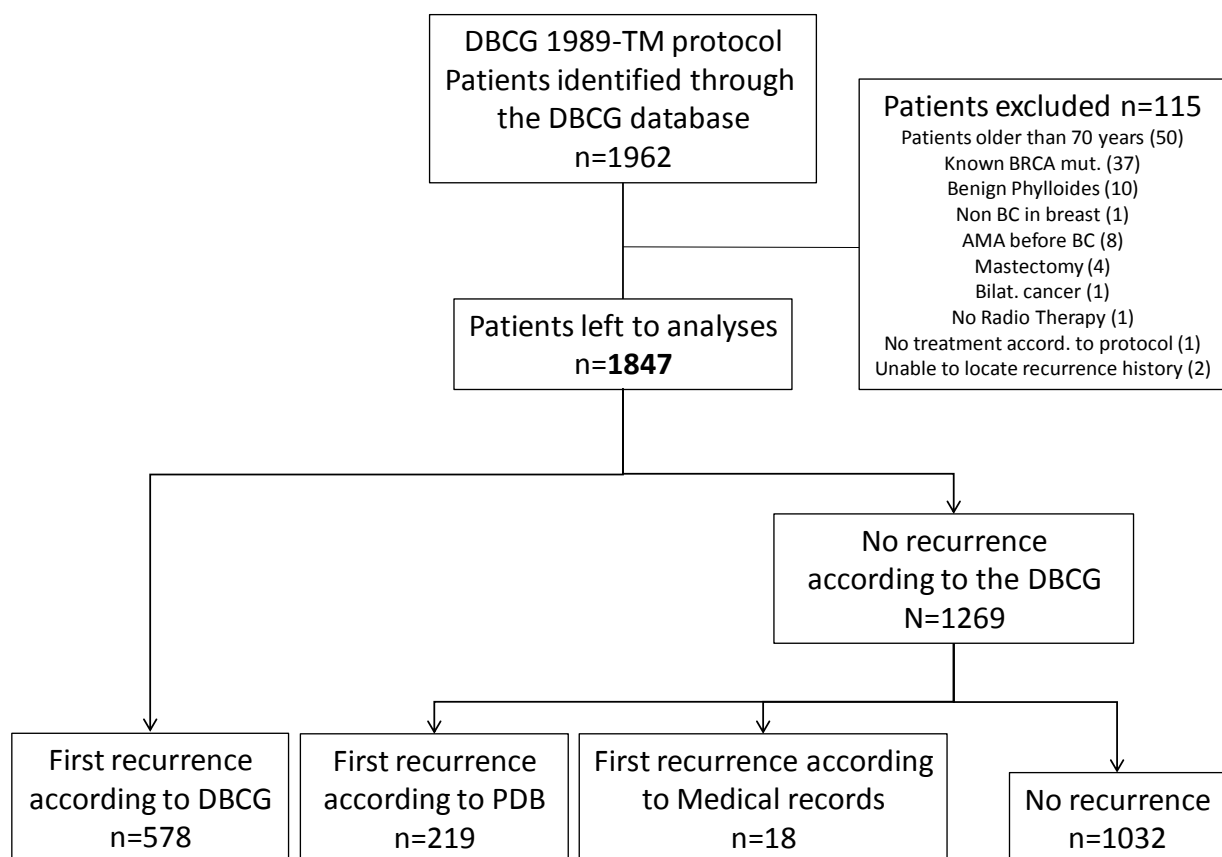
The administration of chemotherapy was adjusted to RT, so that one or two cycles were given before RT, one or two cycles of single-agent cyclophosphamide was given concomitantly with RT, followed by cycles of chemotherapy given until 9 cycles were given in total. Tamoxifen was administered orally, 30 mg once daily, in the prescribed amount of time regardless of RT. Megestrol was administered orally, 160 mg once daily. Pamidronate was administered orally, 150 mg twice daily for 4 years.

Content of the DBCG database:

The database includes patient-, tumor and treatment characteristics: age, menopausal status, date-, place- and type of operation, tumor size, histological type, WHO diagnosis, malignancy grade, ER- and PgR status, and for approximately 30% of the patients: margin status, radiation therapy, adjuvant systemic treatment (none, chemotherapy, anti-hormone therapy, or a combination), localization and date of recurrence, date and diagnosis of other primary cancers, date and cause of premature exit from the clinical follow-up, and date and cause of death. If a patient during the 10 years of clinical follow-up developed a recurrence the patient were registered "off-study" in the DBCG database, from that point of, and thus only the localization and date for a first recurrence were registered. Some patients who experienced a recurrence later than the 10 years of follow-up had also been registered by the attending department to the DBCG.

Details on national Pathology Data Bank:

The national Pathology Data Bank (PDB) contains most pathology examinations on Danish patients since the early 1970's, recorded uniformly, in accordance with Danish guidelines [344]. From 1999 onwards all examinations have been registered online to the PDB from the Danish pathology departments, thus all conducted examinations are available in the data bank [343].



Supplementary figure 1: Overview of inclusion and exclusion of patients into cohort and tracking of events not registered by the DBCG or within the first 10 years of follow-up