

ORIGINAL ARTICLE



Forty years of landmark trials undertaken by the Danish Breast Cancer Cooperative Group (DBCG) nationwide or in international collaboration

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ABSTRACT

Background: Over the past 40 years the Danish Breast Cancer Cooperative Group (DBCG) has made significant contributions to improve outcome and to make treatment of patients with early breast cancer more tolerable through nationwide and international trials evaluating loco-regional and systemic treatments. These trials have been instrumental to establish standards for the treatment of early breast cancer.

Methods: The DBCG 82 trials had a global impact by documenting that the significant gain in loco-regional recurrence from postmastectomy radiation added to systemic therapy was associated with a reduction in distant recurrence and mortality in high-risk pre- and postmenopausal patients. The DBCG trials comparing breast conserving surgery and radiotherapy with mastectomy and more recently the trial of internal mammary node irradiation also had a major impact of practice. The trials initiated by the DBCG 40 years ago on tamoxifen and cyclophosphamide based chemotherapy became instrumental for the development of adjuvant systemic therapy not only due to their positive results but by sharing these important data with other members of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Trials from the DBCG have also been important for highlighting the relative importance of anthracyclines and taxanes in the adjuvant setting. Furthermore, DBCG has made a major contribution to the development of aromatase inhibitors and targeted adjuvant treatment for human epidermal growth factor receptor 2 positive breast cancers.

Results: The substantial impact of these treatment improvements is illustrated by a 46.7% 10-year overall survival of early breast cancer patients treated in 1978–1987 compared to 71.5% for patients treated 2008–2012.

Conclusions: The trials conducted and implemented by the DBCG appear to have a major impact on the substantial survival improvements in breast cancer.

ARTICLE HISTORY

Received 8 September 2017
Accepted 1 November 2017

Introduction

This paper describes how mortality has improved among Danish breast cancer patients in conjunction with improved quality of loco-regional and systemic therapeutic interventions obtained by the major scientific contributions by Danish Breast Cancer Cooperative Group (DBCG) to clinical research.

Loco-regional treatment studies

Mastectomy and radiotherapy

In the early 1970s the Danish standard treatment of early breast cancer patients was simple mastectomy followed by loco-regional radiotherapy as demonstrated in the Copenhagen Breast Cancer study, where patients were randomly allocated to simple mastectomy followed by

radiotherapy or extended radical mastectomy [1–4]. In the DBCG 77 trials the standard treatment was total mastectomy and axillary sampling with the addition of loco-regional radiotherapy in high-risk patients (node-positive and/or invasion to the pectoral fascia and/or T3 or T4 tumors). No systemic treatment was recommended. Orthovoltage was applied ad modum McWhirter, and in 4 out of 5 Danish departments hypofractionation was used due to shortage of radiation capacity [5]. The hypofractionation schedule was a minimum dose of 36.6 Gy in 12 fractions, 2 fractions weekly, or 40.92 Gy/22 fractions, 5 fractions weekly, based on the Ellis NSD formula [6]. A considerable morbidity from hypofractionated orthovoltage radiotherapy was apparent at the time when the early results emerging from adjuvant systemic treatments promulgated the theory proposed by Fisher, e.g., that breast cancer predominantly is systemic disease [7,8]. Thus, there was a shift away from the Halsted theory of

breast cancer being a loco-regional disease, and aggressive surgery/radiation as the only road to cure [9]. The DBCG 82B trial included high-risk premenopausal patients assigned to CMF and DBCG 82C included high-risk postmenopausal patients assigned to one year of tamoxifen, and patients in both trials were randomized to loco-regional radiotherapy versus no radiotherapy. An ethical prerequisite was that in the presence of systemic treatment the patients would not benefit from radiotherapy. As part of the DBCG 82 trial a consensus was reached and implemented nationwide by oncologists specialized in radiotherapy regarding target definition and radiation treatment techniques. The target comprised regional lymph nodes, including the internal mammary nodes (IMN), and chestwall. Electrons was applied against the chestwall plus IMN and the energy was selected according to the distance from skin to pleura by ultrasound, thus the resulting radiation doses to the heart were relatively low. The DBCG 82 trials demonstrated a significant reduction in the risk of loco-regional recurrence and mortality (Table 1) by postmastectomy radiotherapy, irrespective of menopausal status and number of positive lymph nodes [10–13]. These results were confirmed by the EBCTCG meta-analyses and have widely been implemented in international guidelines [14,15].

Breast conservation

The DBCG 82TM (tumorectomy versus mastectomy) trial (Table 1) compared modified mastectomy, or breast conserving surgery (BCS) with residual breast radiotherapy, or BCS with residual breast and regional node radiotherapy [16,17]. No significant difference was seen between the two treatment groups regarding 10-year recurrence-free and 20-year overall survival, $p = .94$ and $p = .24$, respectively. The use of BCS has increased to encompass more than 70% of patients with early breast cancer, as a result of the DBCG 82TM, the associated EBCTCG meta-analysis, earlier diagnosis accomplished by mammography screening, neo-adjuvant systemic treatment, and the use of oncoplastic techniques [18,19]. A population-based study performed by DBCG has documented a high risk of reoperation after BCS for non-palpable breast lesions [20]. Radioactive seed has now been introduced as an alternative to the hook wire localization of non-palpable lesions based on results from a large randomized trial [21].

Fractionation of radiotherapy

The poor results obtained by hypofractionation in the DBCG 77 trials and lack of data supporting superiority of hypofractionation compared to normofractionation, caused a reluctance of the DBCG towards moderate hypofraction in the adjuvant breast cancer setting. In 2002 and 2008, large trials from the UK and Canada testing moderate hypofraction versus normofractionation for breast only radiotherapy showed no difference in local control and a trend towards less late radiation morbidity using hypofractionation [22,23]. However, the patients in these trials were not treated with modern

chemotherapy nor boost, and in the Canadian trial patients with large breasts had been excluded. The DBCG HYPO trial was therefore initiated in 2009 to clarify the possible implications from large breast size, use of tumor bed boost following adjuvant anthracyclines and taxanes. In March 2014, the DBCG standard was modified to 40 Gy in 15 fractions for breast only radiotherapy following a safety analysis including 1883 patients randomized in the DBCG HYPO trial to 40 Gy in 15 fractions compared to 50 Gy in 25 fractions.

In the UK and NL data from the above mentioned trials were extrapolated to patients treated with loco-regional radiotherapy, however, in DBCG this was not accepted. Thus, in 2015 the DBCG Skagen Trial 1 was initiated to introduce moderately hypofractionated loco-regional radiotherapy by randomizing high-risk patients between 40 Gy/15 fractions versus 50 Gy/25 fractions [24,25]. The primary endpoint was arm lymphedema, and secondary endpoints were other morbidities and pattern of recurrence. As of November 2017 around 1100 patients are included, and the trial is expected to accrue around 3000 patients from Europe and Australia.

Partial breast irradiation

In breast recurrences are most often located close to the original tumor bed and the risk of local recurrence has even in high risk patients decreased over decades [26]. Partial breast irradiation (PBI) consequently emerged as an attractive option to lower the radiation burden in selected patients as recently demonstrated in the UK IMPORT LOW trial [27,28]. From 2009 to 2016 the DBCG PBI trial randomized 882 patients to partial versus whole breast radiotherapy and both groups received 40 Gy/15 fractions using the same technique as in the IMPORT Low trial. Early, yet unpublished, results from the DBCG PBI trial regarding morbidity, the primary endpoint, and risk of recurrence are in line with the IMPORT Low trial, and therefore external beam PBI using 40 Gy/15 fractions has since April 2016 been adopted as a standard for selected patients by DBCG.

Treatment of the axilla

During the past 40 years axillary surgery has changed from axillary sampling to axillary lymph node dissection (ALND) and to sentinel node (SN) procedure. Radiotherapy was recommended to lymph node positive patients in the 77 program and this was reinforced by the results obtained in the DBCG 82 postmastectomy trials [10,11]. In a 20-year period ALND partly replaced axillary node level 1 irradiation in node positive patients but the approach of extending radiotherapy to supraclavicular and IMN has been confirmed by others [29,30]. Concern about the possible harmful effect on the heart by IMN radiotherapy and of anthracyclines led in 2003 through 2014 to avoidance of IMN radiotherapy after left-sided breast cancer while IMN radiotherapy was continued following node positive right-sided breast cancer (Table 1). With median 8.9 years follow up an overall survival benefit was shown corresponding to the results in two major trials [29–31]. A meta-analysis of these three studies is in process,

Table 1. Loco-regional treatment, 10-year loco-regional recurrence, disease-free and overall survival.

Study	Regimens	N	LRR (%)	DFS; 95% CI	OS; 95% CI
DBCG 82B	Mastectomy + RT	852	9	48% (45; 52)	54% (51; 58)
Overgaard [10]	Mastectomy	856	32	34% (30; 37)	45% (42; 48)
DBCG 82C	Mastectomy + RT	686	8	36% (32; 40)	45% (41; 49)
Overgaard [11]	Mastectomy	689	35	24% (21; 28)	36% (33; 40)
DBCG 82TM	Lumpectomy + RT	381	7	60% (55; 64)	73% (68; 77)
Blichert-Toft [17]	Mastectomy	350	11	61% (56; 66)	71% (66; 76)
DBCG IMN	IMN + RT	1492	#2.2	#27% (25;30)	#76% (74; 78)
Thorsen [31]	IMN (no RT)	1597	#2.6	#30% (27;32)	#72% (70; 75)

LRR: loco-regional recurrence; DFS: disease-free survival; OS: overall survival; CI: confidence interval; RT: radiotherapy.

#DFS and OS at eight years follow-up.

but international guidelines already have included IMN radiotherapy in their recommendations to high-risk breast cancer patients.

When the SN procedure was introduced just after the turn of the millennium it primarily saved patients with negative nodes from unnecessary morbidity of ALND, but the AMAROS trial suggested that axillary radiotherapy may be substituted for ALND in patients with a positive SN [32–35]. The need of ALND in node positive patients was recently re-challenged and DBCG joined the Swedish led phase 3 SENOMAC trial to evaluate the safety of omitting ALND in patients with one or two positive SN [36].

Long-term outcome and morbidity after loco-regional therapy

The results obtained by BCS and radiotherapy in the DBCG 82TM trial were confirmed in a successive DBCG 89 cohort with similar recurrence and mortality at 20 years [37]. In a small long-term study with a median of 12 years follow-up 88% of the patients were satisfied with their cosmetic outcome, and poor cosmesis was correlated with use of chemotherapy, large breast size and smoking [38]. Local recurrences continued to occur up to 20 years after diagnosis, and a local recurrence in patients <45 years significantly increased the risk of breast cancer mortality, whilst local recurrence among older patients did not [39]. Patients who following a local recurrence developed distant failure could not be identified by classical histopathological parameters or approximated intrinsic subtypes [40]. Efforts to predicting the risk of late morbidity are being continued as part of the DBCG HYPO and PBI trials.

A seven gene profile predicting gain from radiotherapy has been developed using tumor tissue from patients in the DBCG 82 trials and validated in an independent data set [41,42]. Further studies are in progress with the goal to select high risk patients for omission of radiotherapy. Late morbidity was evaluated in a subgroup of patients treated in the DBCG 82 trials [43]. A highly significant gain from loco-regional radiotherapy was seen in patients with 1–3 and ≥4 metastatic nodes and translated into a survival benefit [11–13]. Further analyzes showed that the gain from radiotherapy was highly heterogeneous depending on immuno-histochemical approximated intrinsic subtypes [44].

Very severe late treatment related morbidities are heart disease and second cancer. With 12 years median follow up the DBCG 82 trial did not indicating an increased risk of

radiation induced heart disease, but extensive research on heart disease in Danish and Swedish breast cancer patients documented a dose–response relationship between mean heart radiation dose and risk of major coronary event [45–47]. Recently a hypothesis was proposed correlating smoking and anthracyclines with a very high risk of radiation induced heart disease [48,49]. Second cancer has also been intensely investigated in patients treated according to DBCG guidelines, and second lung cancer is by far the largest risk, the magnitude is around 1:200 in every irradiated breast cancer patient [50]. The results showed that >90% of those patients developing second lung cancer were smokers.

Systemic treatment

Adjuvant endocrine treatment

Along with its metabolites, tamoxifen competes with estrogens for binding to the estrogen receptor (ER) and the early results of a CBCT study suggested adjuvant tamoxifen could reduce breast cancer recurrence and prolong survival following surgery of early breast cancer [51]. The benefits from adjuvant tamoxifen observed in postmenopausal high-risk (node positive and/or T3) patients were validated in the DBCG 77C trial (Table 2). One year of tamoxifen 30 mg daily reduced the risk of recurrence and mortality in patients with ER positive cancers and no benefit was observed in patients with ER negative and PR positive breast cancer [52,53]. One year of tamoxifen 30 mg daily, the standard in the DBCG 89C trial (Table 2), was not inferior to two years of tamoxifen, and a sequence of tamoxifen for 6 months followed by megestrol acetate for six months in postmenopausal high-risk patients [54]. When the Swedish Breast Group trial in 1996 published a beneficial effect from extending tamoxifen from two to five years participants in DBCG 89C still on treatment were offered to extend treatment which may have biased the overall results [55].

The DBCG 82B trial (Table 2) was in pre- and peri-menopausal high-risk patients unable to demonstrate a reduction in the risk of recurrence or mortality from adding one year of tamoxifen to nine cycles of four-weekly intravenous CMF [56]. Corresponding to our results, the first overview published by the EBCTCG in 1988 was unable to demonstrate a benefit from tamoxifen in patients younger than 50 years [57]. With longer treatment duration and follow-up, the benefit of tamoxifen was however by the EBCTCG shown to be largely independent of age, nodal status, and prior

Table 2. Adjuvant endocrine treatment.

Study	Regimens	N	DFS HR; 95% CI	OS HR; 95% CI
CBC 02	Tamoxifen two years	164	0.74; 0.53–1.05 ^a	0.79; 0.63–0.99
Jensen [51]	Placebo	153		
DBCG 77C	Tamoxifen one year	868	0.87; 0.77–0.98	0.83; 0.73–0.94 ^b
Knoop [52]	Control	848		
DBCG 82B	CMF + Tamoxifen	320	0.93; 0.76–1.15	1.05; 0.85–1.30
Andersson [56]	CMF	314		
DBCG 89C	Tamoxifen one year	554		
Andersen [54]	Tamoxifen two years	535	1.04; 0.89–1.22	0.99; 0.85–1.15
	TAM→Megace	526	1.11; 0.94–1.30	1.05; 0.90–1.23
IES	Tamoxifen	615		
Bliss [73]	Exemestane	584	0.84; 0.71–0.99	0.79; 0.66–0.94
BIG 1–98	Tamoxifen	2459		
Regan [71]	Letrozole	2463	0.86; 0.78–0.96	0.87; 0.77–0.999
	TAM→Letrozole ^c	1548	1.07; 0.92–1.25	1.10; 0.90–1.33
	Letrozole→TAM ^c	1540	1.06; 0.91–1.23	0.97; 0.80–1.19
FACE	Anastrozole	2075	0.93; 0.80–1.07	0.98; 0.82–1.17
Smith [76]	Letrozole	2061		
SOLE	Cont. letrozole	2441		
Colleoni [78]	With breaks	2443	1.08; 0.93–1.26	0.85; 0.68–1.07

DFS: disease-free survival; OS: overall survival; CI: confidence interval; HR: hazard ratio.

^aBreast cancer recurrence.

^bBreast cancer mortality.

^cVersus five years of letrozole; TAM: tamoxifen.

administration of chemotherapy and five years of tamoxifen was introduced as a DBCG standard in 1998 [58,59]. The results from aTTOM and ATLAS demonstrated a further incremental benefit from extending tamoxifen to 10 years [60,61]. While tamoxifen in the eighties was considered less effective in premenopausal patients, chemotherapy was thought to be particularly effective and the prevailing view at that time was that this was due to ovarian function suppression (OFS) by chemotherapy [62]. This hypothesis was to some degree confirmed in DBCG 89B that showed a similar DFS and mortality from OFS and CMF [63]. In an exploratory subset analysis the treatment effect largely seemed independent of age, nodal status, tumor size, histological type, malignancy grade, and PR status. However, in the subset with discordant hormone receptor status (either ER or PR negative tumors), CMF resulted in a significant reduction of DFS events and mortality. Several trials support that OFS either alone or in combination with tamoxifen improve outcome similarly to what is achieved with CMF and anthracycline based chemotherapy [64]. Combined the SOFT and TEXT trials demonstrated that OFS with either tamoxifen or an aromatase inhibitor (AI) may lower the risk of recurrence in high-risk premenopausal hormone receptor positive breast cancer patients [65,66]. The cohort study linked to the DBCG 89B trial implied a long-term detrimental effect following OFS corresponding to the data of a long term follow-up of 30,000 participants in the Nurses' Health Study showing an increased mortality despite a reduced risk of breast- and ovarian cancer from ovariectomy in conjunction with hysterectomy due to benign disease [67,68].

In postmenopausal patients aromatase inhibitors have been evaluated in several large trials, and five years of an aromatase inhibitor further reduces mortality by 15% compared to five years of tamoxifen [69]. The breast international group (BIG) 1–98 study compared five years of tamoxifen with five years of letrozole or the two drugs in sequence (each for two to three years) in postmenopausal patients

(Table 2). Initial treatment with letrozole reduced the risk of recurrence and mortality [70,71]. The intergroup exemestane study (IES) recruited postmenopausal women who after receiving adequate local and adjuvant systemic therapy remained free of disease after two to three years of tamoxifen (Table 2). Switch to exemestane for the remainder of five years endocrine treatment reduced the risk of recurrence and mortality [72,73]. A pronounced benefit of upfront aromatase inhibition has been shown in patients with a lobular histology and in patients at a high risk of relapse [74,75]. A comparable result from letrozole and anastrozole was obtained in the Femara versus Anastrozole Clinical Evaluation (FACE) trial (Table 2) and from exemestane and anastrozole in NCIC MA.27 [76,77]. Ongoing clinical trials are evaluating the role of extending endocrine treatment after five years of an aromatase inhibitor and in the meanwhile the study of letrozole extension (SOLE) has shown (Table 2) that continuous extended treatment may be substituted by intermittent aromatase inhibition [78]. Only a small group of postmenopausal patients, i.e., node negative patients older than 60 with grade 1 tumors ≤ 10 mm, will without systemic treatment achieve an age-appropriate survival [79].

Adjuvant HER2 targeted treatment

The addition of a one-year course of trastuzumab to chemotherapy in human epidermal growth factor 2 (HER2) positive disease significantly reduced disease recurrences and mortality in several trials including HERceptin Adjuvant (HERA) trial [80–82]. HERA enrolled 5081 patients; hereof 133 by DBCG, from 2001 to 2005 were adjuvant trastuzumab was introduced as a standard (Table 3). DBCG contributed to international but unfruitful efforts to further improve outcome by extending duration of trastuzumab to two years in HERA and concurrent or sequential addition of lapatinib in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial [83,84]. DBCG

Table 3. Adjuvant HER2 targeted treatment.

Study	Regimens	N	DFS HR; 95% CI	OS HR; 95% CI
HERA Cameron [83]	Trastuzumab two years	1700	0.77; 0.69–0.87	NA
	Trastuzumab one year	1702	0.76; 0.68–0.86	0.74; 0.64–0.86
	Control	1697		
ALTTO Piccart [84]	Lapatinib + T	2093	0.84; 0.70–1.02	0.80; 0.62–1.03
	T→lapatinib	2091	0.96; 0.80–1.15	0.91; 0.71–1.16
	Lapatinib	2100	1.34; 1.13–1.60	1.36; 1.09–1.72
	Trastuzumab	2097		
APHINITY Minckwitz [85]	Pertuzumab	2400	0.81; 0.66–1.00	0.89; 0.66–1.21
	Control	2404		
ExteNet Chan [86]	Neratinib one year	1420	0.67; 0.50–0.91	NA
	Control	1420		

DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; T: trastuzumab; NA: non-available.

Table 4. Adjuvant chemotherapy.

Study	Regimens	N	DFS HR; 95% CI	OS HR; 95% CI
DBCG 77B Ejlertsen [89]	Ctx	181	0.62; 0.46–0.83	0.70; 0.52–0.95
	Oral CMF	193	0.70; 0.53–0.93	0.70; 0.52–0.94
	Control	187		
DBCG 77B Ejlertsen [89]	Ctx	424	0.95; 0.77–1.16	1.09; 0.92–1.29
	Oral CMF	423		
DBCG 82C Ejlertsen [78]	TAM + CMF	709	0.82; 0.71–0.93	0.95; 0.85–1.08
	TAM	736		
DBCG 89D Ejlertsen [95]	CEF	615	0.84; 0.71–0.99	0.79; 0.66–0.94
	CMF	584		
DBCG READ Ejlertsen [101]	EC→D	1001	1.00; 0.78–1.28	1.15; 0.83–1.59
	DC	1011		
BIG 2–98 Oakman [103]	4A→3CMF	481	0.81; 0.67–0.99	0.85; 0.67–1.11
	3A→3D→4CMF	960	1.02; 0.84–1.23	0.96; 0.76–1.21
	4AC→4CMF	487		
	4AD→4CMF	959		

DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; Ctx: oral cyclophosphamide; C: cyclophosphamide; F: fluorouracil; M: methotrexate; A: doxorubicin; E: epirubicin; D: docetaxel TAM: tamoxifen.

investigators enrolled 87 patients in the Adjuvant Pertuzumab and Herceptin in Initial Therapy (APHINITY) trial, which showed a statistically significant reduction in DFS events from the addition of pertuzumab to trastuzumab-based adjuvant therapy [85] but the clinical benefit has yet to be established. Finally, the EXTENDED NERatinib Trial (ExteNET) had participation of 112 patients though DBCG and showed that one year of neratinib, an irreversible tyrosine kinase inhibitor of HER1, HER2 and HER4, compared to placebo further significantly improved DFS when given after one year of trastuzumab-based (neo)adjuvant therapy in HER2-positive breast cancer [86]. One year of trastuzumab added to adjuvant chemotherapy remains standard of care in patients with early-stage HER2-positive breast cancer but neratinib may become an option to some patients [87].

Adjuvant chemotherapy

The achievements of the DBCG with adjuvant chemotherapy has recently been reviewed [88]. In brief, the DBCG 77B trial (Table 4) showed significant and clinically important reduction in the risk of recurrence and mortality from single agent oral cyclophosphamide and from CMF in premenopausal patients with high-risk (node-positive or T3) breast cancer [89]. Adjuvant CMF was in 1982 selected as a standard in high-risk premenopausal breast cancer by DBCG and subsequently in 1985 by the first NIH Consensus development Conference [90]. In a retrospective analysis patients with core-basal and

luminal B breast cancers appeared to derive the largest benefit from cyclophosphamide-based chemotherapy [91]. No apparent benefit was observed from the addition of CMF to tamoxifen among postmenopausal high-risk breast cancer patients in an early analysis of DBCG trial 82C [92] and no clear benefit was shown from adjuvant chemotherapy in the first Oxford overview published in 1988 [57]. A differential benefit however was shown in patients with ER negative breast cancer and adjuvant chemotherapy was in 1989 extended to high-risk postmenopausal patients younger than 70 with ER negative breast cancer. Furthermore, invasive ductal carcinomas with malignancy grade 2 and 3 were irrespective of tumor size and lymph node status included in the premenopausal high-risk group by 1989.

With longer follow-up CMF was associated with a significant improvement in DFS [92,93]. Apart from menopausal status, the DBCG 77B and 82C trials had identical selection criteria, but while 77B trial used classic CMF with oral cyclophosphamide a four-weekly intravenous CMF regimen was used in DBCG 82B and C trials, and a three-weekly CMF regimen was used in the succeeding DBCG 89B and D trials. A population-based DBCG study demonstrated that shifting from classical CMF in DBCG 77B to four-weekly or three-weekly i.v. CMF was associated with a 30% increased risk of a DFS event [94]. Furthermore, the four-weekly regimen as used in DBCG 82B was associated with a 40% increase in mortality.

Danish breast cancer cooperative group 89D showed an incremental reduction in recurrence and mortality from

substituting methotrexate with epirubicin [95]. The advantage of anthracycline-containing three-drug combinations over CMF was confirmed by others and by meta-analysis conducted by EBCTCG, while standard AC (doxorubicin and cyclophosphamide) or EC (epirubicin and cyclophosphamide) for four cycles was not superior to classic CMF [96]. *HER2* and *TOP2A* were assessed retrospectively in 767 of the 980 Danish patients included in DBCG 89D. Topoisomerase II α , the enzyme encoded by *TOP2A*, is a direct target for anthracyclines and essential for resolving topological DNA constraints [97,98]. Alteration of *TOP2A* copy number was in 89D associated with an incremental benefit from epirubicin [99]. This was confirmed in a prospectively planned joint analysis of 89D and four other phase three trials [100] but only a trend toward greater benefit was shown for patients with *HER2*-amplified tumors. The DBCG 07-READ compared six cycles of docetaxel and cyclophosphamide with three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel and confirmed no overall benefit from adjuvant

epirubicin in patients with early and *TOP2A*-normal breast cancer [101]. Other mechanisms of action have been proposed including protection from apoptosis by tissue inhibitor of matrix metalloproteinases-1 (TIMP-1). A highly significant interaction was shown in 89D between epirubicin and a classifier constructed by combining lack of TIMP-1 expression and/or *TOP2A* alteration [102].

In BIG 2-98 (Table 4) a further reduction in the risk of recurrence was obtained from adding a taxane to sequential anthracycline and CMF but not from substitution of cycles of cyclophosphamide and doxorubicin with docetaxel and doxorubicin [103]. Similarly a further reduction in breast cancer mortality appeared in the EBCTCG meta-analysis from the addition of a taxane to a standard AC, while the substitution of cycles or drugs with a taxane was not associated with a reduction in mortality [96]. ECOG 1199 in a factorial 2 by 2 design showed a superior benefit from weekly paclitaxel compared to three-weekly and from three-weekly docetaxel compared to weekly, and overall no difference between docetaxel and paclitaxel [104].

Results

Overall survival is in Figure 1 presented according to period of diagnosis for all patients with operable invasive breast cancer, irrespective of the received loco-regional and systemic treatment. A major and clinically important improvement in prognosis according to period of diagnosis is apparent with a decrease in 10 year mortality from 53.3% in 1978–1987 to 28.5% for those diagnosed in 2007–2015 (Figure 1).

A temporary setback in the otherwise continuous improvement in prognosis occurred in the second half of the 1978–1987 period as a consequence of a less effective adjuvant CMF regimen and omission of postmastectomy radiotherapy in patients randomized to the control group in the DBCG 82B&C trials. The improvements obtained in the succeeding periods can hardly be attributed to a single treatment or trial (Figure 2). The proportion of patients receiving adjuvant treatment increased from none to more than 80%, the proportion of patients who received chemotherapy in combination with endocrine therapy and/or trastuzumab increased and the distinct treatment regimens evolved as described in Figure 2 and the preceding sections.

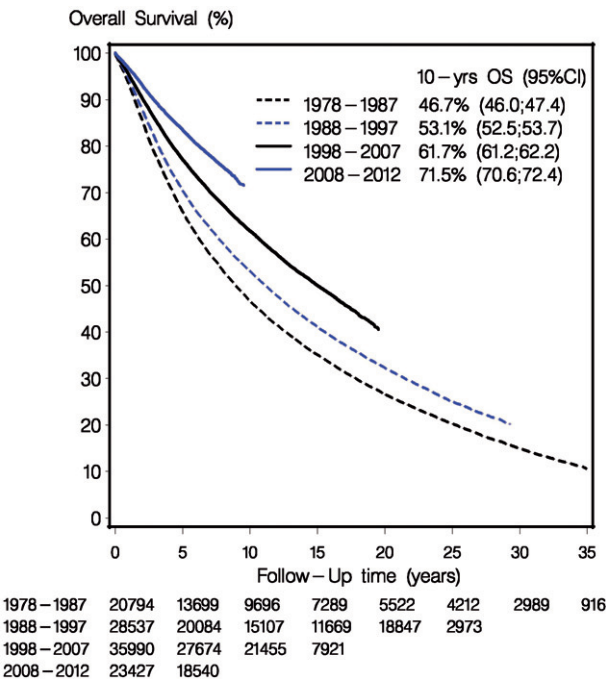


Figure 1. Overall survival (OS) according to period of diagnosis. All patients, irrespective of adjuvant treatment.

Period	1978 – 1987	1988 – 1997	1998 – 2007	2008 – 2015
Endocrine therapy				
Premenopausal	None		Tamoxifen 5-yr	Tamoxifen 10-yr
Postmenopausal	Trial only	Tamoxifen 1-yr	Tamoxifen 5-yr	AI or AI->TAM 5-yr
Anti-HER2 therapy				
	None	None	Trial only	Trastuzumab 1-yr
Chemotherapy				
Premenopausal	Trial only	CMF or CEF	CEF	EC->taxane
Postmenopausal	None	CMF in ER negative	CEF in ER negative	EC->taxane

AI: aromatase inhibitor; C: cyclophosphamide; M: methotrexate; E: epirubicin; F: fluorouracil

Figure 2. Patients and treatments in successive decades.

Discussion

In this nationwide and population-based study we have demonstrated a significant improvement of the prognosis following early breast cancer in four successive decades. Furthermore, the present study indicates that the substantial reduction in mortality from 53.3% to 28.5% in first 10 years after breast cancer is closely connected to results obtained in clinical trials and in particular to those obtained by the Danish Breast Cancer Cooperative Group nationwide or in internal collaboration. In a study accompanying our study in this issue a quite fast implementation of guideline modification is shown over the last decade and equivalent results have previously been shown for the preceding three decades [105,106].

Several issues should be considered when interpreting this study. First, the population-based design of our clinical database and the prospective and comprehensive registration of patients and treatments minimized the risk of bias. Second, patients above 70 at diagnosis of breast cancer and patients with multimorbidity were not included in phase 3 trials and results from clinical trials may not have been implemented fully in non-eligible patients. Third, life-expectancy has gradually been increasing during the last four decades and may in part explain our results. Finally, earlier diagnosis and alterations in the biology of the disease may have contributed to reductions in mortality.

Disclosure statement

No potential conflict of interest was reported by the authors.

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