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REVIEW

An overview of prognostic factors for long-term survivors of breast cancer

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Abstract
Background Numerous studies have examined prognostic factors for survival of breast cancer patients, but relatively few have dealt specifically with 10+-year survivors.
Methods A review of the PubMed database from 1995 to 2006 was undertaken with the following inclusion criteria: median/mean follow-up time at least 10 years; overall survival and/or disease-specific survival known; and relative risk and statistical probability values reported. In addition, we used data from the long-standing Eindhoven Cancer Registry to illustrate survival probability as indicated by various prognostic factors.
Results 10-year breast cancer survivors showed 90% 5-year relative survival. Tumor size, nodal status and grade remained the most important prognostic factors for long-term survival, although their role decreased over time. Most studies agreed on the long-term prognostic values of MI (mitotic index), LVI (lymphovascular invasion), Her2-positivity, gene profiling and comorbidity for either all or a subgroup of breast cancer patients (node-positive or negative). The roles of age, socioeconomic status, histological type, BRCA and p53 mutation were mixed, often decreasing after correction for stronger prognosticators, thus limiting their clinical value. Local and regional recurrence, metastases and second cancer may substantially impair long-term survival. Healthy lifestyle was consistently related to lower overall mortality.
Conclusions Effects of traditional prognostic factors persist in the long term and more recent factors need further follow-up. The prognosis for breast cancer patients who have survived at least 10 years is favourable and increases over time. Improved long-term survival can be achieved by earlier detection, more effective modern therapy and healthier lifestyle.

Keywords Breast cancer · Long-term · Prognostic factors · Survival

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Introduction

Breast cancer (BC) is the most common cancer among women, with a lifetime risk of up to 12% and a risk of death of up to 5% [1]. Its incidence has been increasing but after a period of continuous rise in many industrialized countries BC mortality has been stable or has even decreased in the last 10–15 years [2, 3]. The introduction of mass mammographic screening programmes also resulted in earlier detection and diagnosis of small and less aggressive tumours. This, in combination with therapeutic improvements, has led to a substantial increase in BC survivors over the last few decades (Fig. 1). A long-term survivor is commonly defined as a person who is still alive 5 years after cancer diagnosis [4]. For BC, the relative

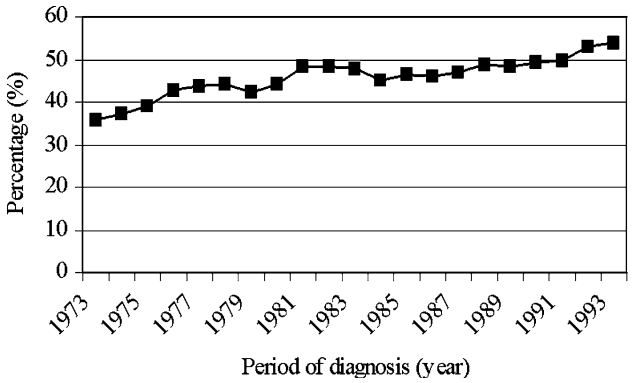

Fig. 1 Proportion of breast cancer patients (3-year moving average) diagnosed between 1973 and 1993 who survived 10 years or longer in Southeastern Netherlands

survival at 5 and 10 years after diagnosis is 88% and 77%, respectively, both substantially higher than the 5-year relative survival of all cancers together (64%) [4]. Thus, it seems logical to consider factors known to play an important role in predicting 5-year survival of BC patients and to question their importance in survival 10 years after diagnosis and even longer. Furthermore, in recent years major advances in the prognostic value of several molecular markers have been achieved, hence the need to incorporate this data into our current knowledge. Therefore, we have summarized available knowledge on the determinants of survival 10 years or more after breast cancer diagnosis. We supported our analyses and considerations with data from the population-based, long-standing Eindhoven cancer registry in the Netherlands.

Methods

We initially searched PubMed, using the search MESH term for 'breast neoplasms' AND 'prognoses' AND 'long-term'. Only papers published in English between 1995 and 2006 (September) which researched female adults (19+ years) were included. We retrieved 528 articles and studied the abstracts (sometimes also the methods section). We selected only articles that assess or show the results for those surviving 10 years or longer with cohorts having a mean/median follow-up of 10 years or longer. If mean/median follow-up time was not reported, we examined the proportion of patients who survived 10 years after diagnosis, and this ought to be larger than 50%. If, for a specific topic of interest, no relevant studies with a follow-up of at least 10 years were found (such as BRCA mutation or gene profiling, which have been studied only during the last decade), then studies with the longest available follow-up were chosen. Furthermore, the following inclusion criteria were used: overall and/or BC-specific survival was reported; relative risk or hazard rate and statistical probability values were given; at least 250 BC patients included at the beginning of study. We also searched the reference lists collected by this search strategy and selected those that were relevant to both our study question and inclusion criteria. Reviews and books that gave general overviews were also included in the reference list.

We present data from the Eindhoven Cancer Registry (ECR) to illustrate the role of factors such as age, tumour size, lymph node involvement and time since diagnosis. Within the Netherlands, ECR is unique because it has collected follow-up data since 1970, including clinical aspects of cancer patients. This is a population-based cancer registry covering a population of almost 2.4 million people in 2004 [5]. Cumulative survival proportion was calculated using the Kaplan Meier method. Relative survival was calculated by comparing the survival of BC patients to the general population.

Throughout the text the term long-term and/or survival will frequently be mentioned; this corresponds to at least 10-year survival unless otherwise indicated.

Results and discussions

Determinants of survival BC 10 years or longer

Patient characteristics

Age at diagnosis Very young women, i.e. younger than 30/35 years [6, 7], exhibited a particularly poor survival as do those older than 70 (Fig. 2) [8, 9]. Young BC patients were more likely to have a more negative clinical presentation, such as affected lymph nodes, negative for oestrogen receptors, and have large tumour with a high fraction of p53 nuclei and overexpression of c-erb-2 oncoprotein [6, 10, 11]. However, current adjuvant treatment seems to diminish the poor prognostic value of young age [6]; young women who did not receive adjuvant treatment had a significantly increased risk of dying; those diagnosed at 35–39 years and <35 years had a 1.4 and 2.2 higher risk of death, respectively, compared to those of 45–49 years [6]. Older patients exhibited higher mortality rates [12], probably because of less extensive treatment (either related to advanced age itself or the presence of serious concomitant diseases (comorbidity)) [13].

Comorbidity Concurrent health conditions (comorbidity) at the time of BC diagnosis have a significant impact on early [13] as well as long-term survival of BC patients [12]. The most prevalent conditions were cardiovascular disease (7%), previous cancer (7%) and diabetes mellitus (6%), all

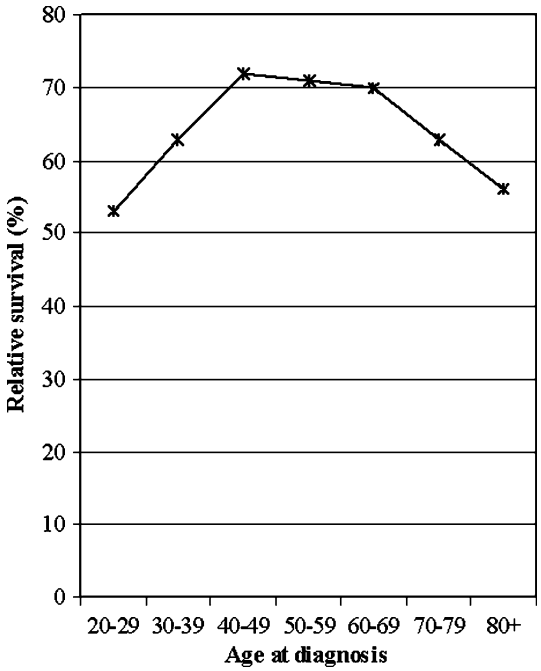

Fig. 2 Relative survival of breast cancer patients (n: 13,279) diagnosed in 1990–2002 and followed until 2004, according to age at diagnosis in southeastern Netherlands

becoming more common with increasing age [13]. Compared to those without comorbidity whose 5-year relative survival was 87%, those with diabetes mellitus or cardiovascular disease represented 78% and 83% of the respective survival estimates [13]. Patients with severe comorbidity exhibited a 2.7–3.4 higher risk of death in 10 years compared to those without comorbidity [12, 14].

Period of diagnosis Access to care and treatment of BC has improved over time in most industrialized countries, which is reflected in the higher long-term survival of BC cases across all age groups and the tumour characteristics of those diagnosed more recently [15–18]. In Finland, relative survival 10 years after diagnosis among patients younger than 50 years increased from 49% for those diagnosed in 1953–1959 to 68% for the 1983–1989 cohort [15]. Furthermore, 60% of node-positive BC patients diagnosed in 1978–1979 in Italy survived 10 years or longer compared to the 50% probability 10-year survival for those diagnosed in 1968–1969 [17]. In addition, changes in BC diagnosis, e.g. screening[19, 20] and better staging [17], may partly be responsible for the observed increase in the proportion of survivors.

Time after diagnosis The longer a woman survives BC the more the prognosis improves, illustrated by conditional survival [16, 21]. Probably the subgroup of patients who

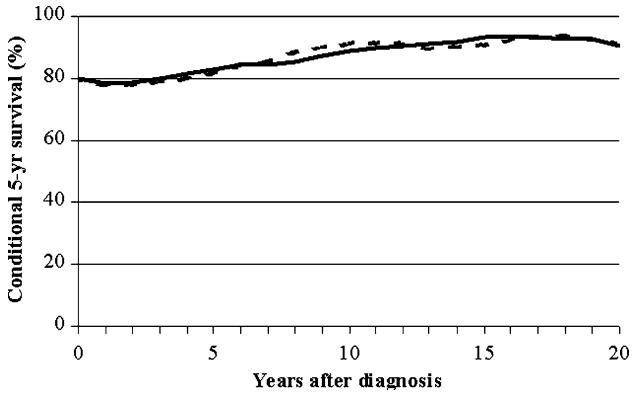

Fig. 3 Conditional 5-year relative survival (calculated using period analysis [22] of breast cancer patients diagnosed in southern Netherlands in 1985–2002 and followed until 2004, according to age. (*Dashed line*): diagnosed at 25–49 years, (*solid line*): diagnosed at 50–74 years

survived longer had less aggressive tumours due to a different genetic make-up or better life-style. In Australia, 79% of women with localized BC survived 10 years after diagnosis, yet among those still alive 5 years after diagnosis 84% had a 10-year survival [16]. The respective values for regional vs. advanced BC were 53% and 68% [16]. Unlike other cancers, relative conditional survival remained stable below 100% after 12 years of survival and decreased again after about 19 years (Fig. 3) [5]. This may be a consequence of late recurrences and metastases, second cancers or late side-effects of treatment [23].

Socioeconomic status (SES) and race A population-based study of BC patients diagnosed in 1968–1999 in France showed a diminishing role of SES on excess mortality among women with BC over these periods [24]. Long-term follow-up studies reported that women with BC from low social classes had a 20–50% poorer survival compared to patients from higher social classes [25, 26], although others contradicted this [27]. Low SES patients were more likely to be diagnosed at a later stage, had more aggressive tumour characteristics and might have received sub-optimal treatment. However, differences in these prognostic factors did not fully explain the variation in survival according to social class [25]. This is also the case when breast cancer survival is studied according to race/ethnicity. Ten years after treatment 58% of African Americans were still alive compared to 66% of the white Americans. After adjusting for other prognostic factors, 41% excess mortality from all causes was still observed among African Americans compared to caucasians [28]. This suggests other residual factors such as lifestyle (higher body weight was observed among African Americans), comorbidity [14], genetics or variation in the delivery of treatment, which influence outcome beyond variation in tumour aggressiveness [29].

Tumour-related characteristics

Tumour size Tumour size is one of the strongest prognostic indicators (Fig. 4) [7, 30], even after 20 years of follow-up [8, 31]. A larger tumour has been related to more positive lymph nodes [32], thus their interaction further influences the survival from BC. Nonetheless, the independence of survival by node status is shown by the lower 10-year overall survival rate found for node-negative patients with a tumour of 2–5 cm compared to those with a tumour smaller than 1 cm, 66% vs. 79%, respectively [33].

Histological type The prognostic value of histological type can be grouped into four: excellent, good, poor and very poor prognosis [34]. BC with an excellent prognosis, such as invasive cribriform, tubular [35], tubulo-lobular and mucinous [36, 37] showed >80% survival at 10 years [9]. Tubular mixed, mixed ductal with special type, atypical medullary [38] and alveolar lobular carcinoma have a good prognosis with a 60–80% 10-year survival. Those with invasive papillary, classic lobular and medullary cancers have a worse prognosis. Finally, 10-year survival among those with ductal, solid lobular, mixed ductal and lobular carcinoma is below 50% [34]. In most populations infiltrating ductal carcinoma covers about 70% of all diagnoses [36, 39]. Inflammatory BC has a particularly poor prognosis: about 30% survived 10 years [40].

Histological grade The most widely used grading systems are Scarff-Bloom-Richardson classification, Fisher grading nuclear system and Nottingham Combined Histologic Grade (NCHG) [41]. The validity of grading has been subjected to inter-observer reproducibility and subjectivity [42]. However, higher grades have been quite consistently associated with lower long-term survival [7, 8, 31, 43–45]. Depending on other prognostic factors, such as nodal status or tumour size [46, 47], cumulative survival among patients with the lowest score was 90–94% 10 years after diagnosis and 30–78% among those with the highest score [37, 48].

Regional lymph node involvement Lymph node involvement is a valuable indicator of long-term survival (Fig. 5) [8, 32]. Node- positive patients have about a 4–8 times higher mortality than those without nodal involvement [8, 9, 49]. The more nodes involved the worse the prognosis. Prognosis for patients with 10 or more involved axillary nodes showed 70% more deaths at 10 years than for those with 1–3 involved nodes [32]. The survival of node-positive patients improved due to better staging procedures and application of systemic treatment [7, 31, 50].

Lymphovascular invasion (LVI) and molecular markers of tumours angiogenesis At the St. Gallen meeting in 2005, LVI was added to the prognostics for node-negative patients [51]. Compared to patients having no LVI, a 60% higher BC mortality was observed for node-negative BC patients having positive LVI [52, 53], although others did not observe the independent role of LVI [46, 50]. In this line of research, studies have also focused on the value of microvessel density [44], blood invasion (BVI) [54] and markers of angiogenesis (VEGFR (vascular endothelial growth factor receptor), CD105, Tie-2) [55, 56] in predicting long-term survival of BC patients, although the results are still conflicting.

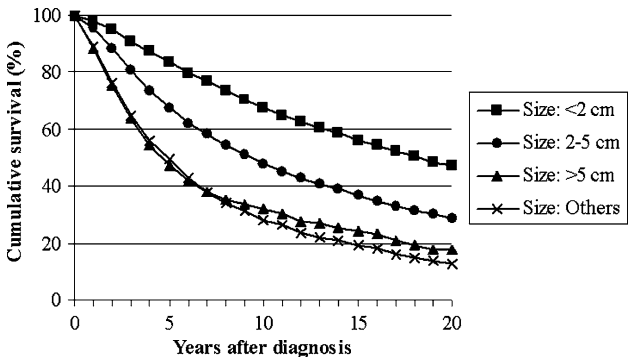

Fig. 4 Cumulative survival proportion of breast cancer patients diagnosed in southern Netherlands in 1970–1994 and followed until 2004, according to tumor size (based on pathological diagnosis). ■ tumor size: <2 cm (n: 3263) • tumor size: 2–5 cm (n: 3420) ▲ tumor size: >5 cm (n: 474) **x** tumor size: involvement of skin (n: 1133) and unknown/not applicable tumor size: 1410

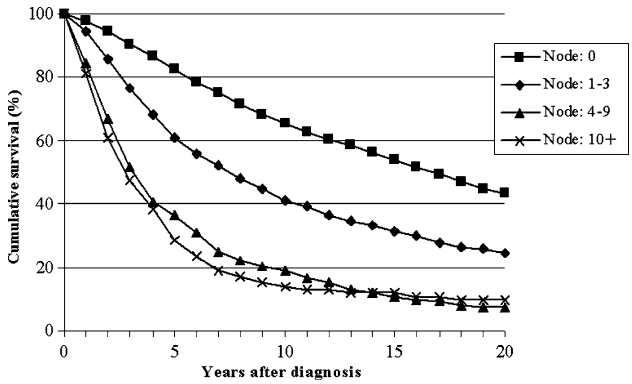

Fig. 5 Cumulative survival proportion of breast cancer patients diagnosed in southern Netherlands in 1970–1994 and followed until 2004, according to nodal status (based on pathological diagnosis). ■ node negative (n: 4452) • node status: 1–3 positive nodes (n: 3266) ▲ node status: 4–9 positive nodes (n: 255) **x** node status: 10+ positive nodes (n: 189), unknown/not applicable node status: 1538

Grouped prognostic factors Some of the prognostic factors have been combined into a prognostic index, such as the TNM classification and also the more current Nottingham Prognostic Index (NPI), both highly predictive for estimating long-term survival [41]. TNM staging consists of information on primary tumour size, involvement of the regional lymph node and the presence of distant metastasis. Only 53% of patients with regional or locally advanced BC had survived 10 years after diagnosis compared to 79% of those with localised BC [16]. Patients with metastasis (stage: M1) at diagnosis exhibited very poor 10-year survival (3.4%) [57].

Tumour size, grade and lymph node status make up the NPI [11, 46, 49]. In a large series of 2879 BC patients, 10-year survival proportion was 85% for those with the lowest NPI score and 19% for those with the highest score [11].

Recurrence, metastasis and second cancer

Patients with recurrent, metastasized or second cancer generally exhibited lower long-term survival than those without [9, 21, 58–61]. Ten years after surgery, the probability for survival for another 10 years, thus 20 years after diagnosis, for node-negative patients aged ≥45 years, tumour ≤1 cm, grade 1 and without a recurrence or metastasis was 0.89. If a recurrence occurred, the probability of being alive at 20 years dropped to 0.72. If a metastasis was observed the probability of survival was only 0.18 [21]. The prognosis decreases with larger primary tumour size, nodal involvement [62], higher grade,[21] early recurrence (within 5 years of surgery)[63], location of recurrence (regional rather than local ipsilateral) [59] and inadequate primary cancer treatment [9, 64]. In the dataset of the ECR, overall survival was better for women without second primary tumours than for women who developed a new primary cancer (Fig. 6). Only 68% of early BC patients with second malignancies had survived 10 years of follow-up compared to 78% of those without multiple cancers [65]. Younger BC patients are reported to have poorer survival and a higher risk of second cancer [59]. Corrected for race and grade, women in the 20-29 year old category who had a second BC had a probability of 10-year survival probability of only 23% compared to 57% for those without multiple cancers.

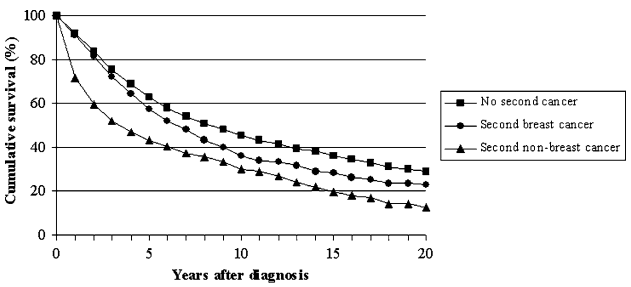

Fig. 6 Cumulative survival of breast cancer patients diagnosed in southern Netherlands in 1970–1994 and followed-up until 2004, according to second cancer. Follow-up for patients with second cancer begins at the date of second cancer diagnosis. ■ no second cancer (n: 8137) • second breast cancer (n: 744) ▲ second non-breast cancer (n: 819)

Other tumour markers

Hormone receptors The presence of hormone receptors such as oestrogen (ER) and progesterone (PR) receptors predicts the long-term outcome of hormonal therapy [66], thus they have been more commonly used as a predictive marker rather than as a prognostic marker. Thus given a particular treatment, e.g. tamoxifen, ER-positive patients have a considerably better prognosis than ER-negative patients. The prognostic value is weak [30, 43] or negligible [37], particularly in the early years after diagnosis [67].

HER-2 expression Node-positive patients with BC cells showing amplification of the gene for human epidermal growth factor receptor type 2 (HER2), and/or overexpression of its product had a lower 10-year overall survival proportion, 50% versus 65% for those without HER2 amplification [17, 68]. After 10 years the difference in survival persisted, although it became somewhat smaller[17]. Tumours that overexpress HER2 are more likely to contain p53 abnormalities, to be hormone receptor- and bcl-2-negative and to have lymphoid infiltration and a high mitotic index, all known to be markers of poor prognosis for BC [17, 69, 70]. As for patients with node- negative tumours, HER2 did not seem to affect long-term survival significantly [17, 37, 69]. HER-2 expression has been valuable in predicting treatment responses to trastuzumab, certain endocrine therapies and chemotherapy, adding to it's role as a predictive marker [68].

Mitotic Activity Index (MAI) MAI is an indicator of tumour proliferative activity that represents the mitotic activity in a given area of the tumour. Combined with another prognostic factor (NCHG), MAI has proven to be an accurate tool for assessment of long-term survival [48]. In a population-based study women with node-negative tumours <5 cm and a MAI ≥10 exhibited 80% survival at 10 years compared to 90% for an MAI <10 [71].

Gene expression profile A very promising new finding is the microarrays method, in which a set of intrinsic genes is

clustered and segregated into major subgroups; BC with a good and poor prognosis profile is correlated to the probability of distant metastases [72] or a tumour with basal or luminal characteristics which are strongly associated with ER status [73]. In a study of 295 patients diagnosed with stage I or II breast cancer, those classified as having a good prognosis profile had a 95% overall 10-year survival rate compared to 55% for those with a poor profile [74]. This classification predicted outcome regardless of the nodal status, implying that more accurate criteria have become available for administering adjuvant systemic treatment.

Various molecular markers BRCA1 & 2 mutations were first identified in 1994 and are BC risk factors for some specific groups [75]. Their role as prognostic indicator for long-term (more than 10-year) survival has not yet been established. A study of 496 women (median follow-up: 116 months), 56 of whom (11%) carried a BRCA1/BRCA2 mutation, showed worse BC-specific survival for women with BRCA1 mutations than for those without (62% at 10 years versus 86%; $P < 0.0001$), but not for women with the BRCA2 mutation [76]. However, another study which compared patients from BRCA1, BRCA2 and non-BRCA1/2 families as well as sporadic cases did not confirm the prognostic role of BRCA1/2 [77].

Long-term follow-up studies have not demonstrated an independent effect of p53 mutations on long-term survival. The P53 mutation was related to a poor clinical profile for patients, hence in multivariate analysis its role on survival diminished [10, 69, 78, 79].

A high level of tissue urokinase-type plasminogen activator (uPA) and its inhibitors has been correlated with poor outcome for node-negative and node-positive patients. Those having the highest level of uPA have a five times greater risk of dying from BC compared to those with the lowest level [69]. Other factors such as Ki67 (MIB-1), cathepsin-D, DNA ploidy and S-phase have been suggested as prognosticators of survival, with conflicting results, particularly among long-term survivors. Their use in general clinical settings is therefore not recommended [80, 81].

Miscellaneous

Lifestyle Generally, increased death rates due to BC (13–20%), other causes (49–86%) and all causes (14–70%) have been observed among obese patients [82–85]. Normal body weight tended be more beneficial in death from other causes than from BC: [83, 84] 9.5% of obese patients died from non-BC causes compared to 6.4% and 5.8%, respectively, of the normal or intermediate groups [82]. Obesity was also related to a 2-fold increased risk of postmenopausal contralateral BC and a 60% higher occurrence of second other cancers [84]. Therefore, normal weight may reduce the risk of second post-menopausal BC, second other cancers and overall mortality [83, 84, 86].

Compared with women who engaged in less than 9 metabolic equivalent task (MET)-hours per week of activity, women who engaged in 9 or more MET-hours per week had a 40% lower risk of death from all causes, translating into a 6% absolute (unadjusted) reduction in mortality [87], which emphasizes the need to advise physical activity.

So far, although studies have not convincingly shown the positive influence of eating fruit, vegetables and soy bean on long-term BC survival [85, 88], diets high in fruits, vegetables, legumes, poultry, and fish and a low intake of red meat, desserts and high fat dairy products are likely to protect against mortality from non-BC causes [89].

Modification of BC's prognostic factors

Various studies have questioned the role of BC risk factors in determining the biological tumour features as mentioned above. Indeed, BC risk factors seem to differ according to histological type, grade, size, nodal status and ER/PR receptor status [90–93]. For example, excessive alcohol intake and obesity increased the risk for the development of ER-positive tumours [92, 93]. As for late age at first full-term birth and obesity are related to an increased risk of large tumours [91]. Hence, risk factors for BC may also affect breast biology and clinical behaviour, thus also BC prognosis.

Changing importance of prognostic factors over time after diagnosis

Commonly, the value of prognostic factors decreases depending on the length of the follow-up period [31, 94]. Survival curves according to prognostic factors usually show a large drop in survival for all stages during the first 5 years; afterwards the curve stabilizes. Studies agreed on the long-lasting influence of tumour size at diagnosis on survival, albeit attenuating over time [31, 94, 95]. Grade, nodal status and metastases were also valuable in predicting survival up to 20 years after diagnosis [31, 95]. Although, others have reported that 10 years after diagnosis only tumour size [94] or nodal status [8] or old age [8] remained as an independent predictor of long-term survival. Similarly, ER/PR status and MAI only had a significant prognostic role in the first 5–10 years after diagnosis [67, 71, 96]. Because even 10 years after BC diagnosis the probability of survival for BC patients does not seem to reach that of the general population, the role of

Table 1 Overview of studies reporting long-term prognostic factors for breast cancer (BC) patients

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
1	Haerslev and Jacobsen 1995 [70][a]	490	10.6	MS, T, N, Htyp, MI, G, PR, Her2	All patients: N & PR In N+: MI & PR In N-: MS & G	Her2	Overall survival was measured. P53 was related to absence of tubular formation, high G, ER-negative, high PCNA (proliferating cell nuclear antigen) score
2	Pietilainen 1995 [10]	392	11.1	P53, N, T, Htyp, tubular formation, intraductal growth, margin formation, necrosis, DNA ploidy, S-phase fraction	All patients: N, T, MI In N+: T, MI In N–: T, p53, G		Overall survival was measured. P53 is related to younger age, MI, AI, G, nuclear pleomorphism
3	Haerslev 1995 [79][a]	490	11	PCNA	T, G, PR	Her2 & PCNA (Proliferating cell nuclear antigen)	Overall survival was measured. PR was only an independent factor in N-positive pts. Her2 & PCNA were related to more positive N, higher G, ER-/PR-negative
4	Gamel 1996 [39]	163,808	NR. Range 1mos-19 yrs	Histological type by stage (localized & regional BC)			Breast cancer specific survival was measured
5	West 1996 [12]	1196	NR. Diagnosed: 1973–1986. End FU: 1994.	Comorbidity	Level of comorbidity	Adjusted for age, race, stage, N, therapy. Values for these factors were not shown	Overall survival was measured. Charlson comorbidity index was used. There is no difference in the significance of comorbidity on survival of Caucasians and African American (AA)
6	Haerslev 1996 [112][a]	487	>10	Ki-67, PCNA	T, G, PR	Ki-67 & PCNA.	Overall survival was measured. PR only an independent factor for N+ patients. Ki-67 was related to T, MI, G
7	Northridge 1997 [36]	Mucinous BC: 4082. Infiltrating duct BC: 139,154	NR. Diagnosed: 1973–1990		HTyp, period of diagnosis, Stage, G	Age	Breast cancer specific survival was measured
8	Kollias 1997 [11][a]	2879 age ≤70, T <5cm	>10	Age <35, NPI	T, G, N	Age	Overall survival was measured. Younger than 35 yrs had higher grade, more LVI and worse NPI group. After 10yrs NPI did not change OS

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
9	Zahl and Tretli 1997 [95]	8802 age <70	Diagnosed: 1965–74. End FU: 1991	Survival categorized by age, stage and follow-up time			Excess hazard from breast cancer was measured. After 8 yrs being younger than 35 does not influence survival. Stage was an important prognosticator up to 20 yrs
10	Pinder 1998 [47]	465	12	N by grade, Treatment by grade			Overall survival was measured. The study aimed to confirm value of Nottingham grading system for survival. N+G3 patients benefited from prolonged chemotherapy
11	Gaffney 1998 [113]	BRCA1: 30 BRCA2: 20 Control: 18278 BC pts	BRCA1: 9.8 BRCA2: 7.5 Control: NR			BRCA1 vs. BRCA2 vs. control	Overall survival was measured Case and control were matched for date of birth, date of diagnosis and tumour size. Patients with BRCA+ were younger. Patients with BRCA1 had higher grade
12	Wojcik 1998 [28]	6577 patients Whites: 5879 African American (AA): 698	At 10 yrs 59–67% patients were alive	Race, G, N, T, stage, waiting time, smoking, being a widow, having other family as dependent	Race, age, stage	UV: alcohol, family history	Overall survival was measured. AA is more likely to be younger at diagnosis, have larger tumour, higher stage and more lymph nodes
13	Mansi 1999 [114]	350	12.5	Bone marrow micrometastases	N, T	Bone marrow micrometastases, LVI	Overall and breast cancer-specific survival was measured. Bone marrow metastases may be useful as prognostic factor for BC pts without information on T and N
14	Kollias 1999 [46][a]	319 T ≤1cm	>10	G, N, LVI, NPI	G, N	LVI	Overall survival was measured
15	Tabar 1999 [45]	2468	NR. Diagnosed: 1977–85. End FU: 1996	T, N, G, detection mode, HTyp	TXN, age*N, Htyp*N, T*N*G		Overall survival was measured. Screening arrests disease progression. Tumour progression is more rapid in BC patients <50 yrs. OS of T1a(1–5 mm) vs. T1b(6–10 mm) NS.

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
16	Holmes 1999 [85]	1982	13.1	BMI ≥30	3rd to 5th quintile of protein protein intake after diagnosis, N, T, G	BMI, protein intake prior diagnosis, alcohol intake	All cause mortality was measured. MV for BMI was corrected for age, diet interval, oral contraceptive use, hormone replacement therapy, MS, age at menarche, aget at birth and parity, smoking, T, G, N, ER, PR BMI <21 and 1st quintile of protein intake were reference. Significant trend of higher mortality from lowest to highest quintiles of fibre, lutein and zeaxanthin, calcium and protein intake, with 13–35% lowest mortality in the lowest quintile
17	Nomura 1999 [58]	1857 <80 yrs stage I-III	12	Second cancer and recurrence	Age, ER, N, recurrence, second cancer		Overall survival was measured Recurrence is related to higher stage, younger age at diagnosis, Htyp, and therapy. Second cancer is related to younger age. Death related to recurrence and second cancer is increased 12 yrs after diagnosis.
18	Reed 1999 [37]	613 T1-2N0	15.5	Age >50, T, G	G, T, treatment	UV: treatment, ER, PR, Her2, P53	Overall survival was measured. Her2 was related to PR-, ER-negative, P53, G. P53 was related to PR-. Treatment was ovarian & locoregional irradiation that had lower mortality rate
19	Aebi 2000 [7]	3700 pre- & perimenopausal	12	Age <35 vs. ≥35	N, T, G, age <35*ER+	Age, ER	Overall survival was measured. Younger patients with ER+ who were not amenorrhoea had a significantly shorter survival
20	Ferrero 2000 [78]	297 N-	11	T, ER, P53	T, ER	Age, PR, G	Breast cancer-specific survival was measured. P53 was related to grade, T, ER-negative. P53 was continuous variable

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
21	Kroman 2000 [6]	10,356 age <50	NR. Diagnosed: 1978–96.		Age, T, N, G	Period of treatment and surgery	Relative survival was measured for excess mortality due to BC. When chemotherapy was given BC at young age does have worse prognosis
22	Ferrero-Pous 2000 [69]	488	10	ER, uPA, G, N, PR, P53 by Her2	All patients: uPA, N, T, Her2, age In N–: uPA, T In N+: N: uPA, T, age, Her2		Overall survival was measured. For patients who received chemotherapy uPA, T & N determined OS. For patients who received hormonal therapy uPA, Her2 & N determined OS
23	Kato 2001 [44][a]	377	10	T, N, G	AMC, T, N, G	Necrosis	Overall survival was measured. AMC is a good prognostic factor for N- and T2-3 patients
24	Liu 2001 [96]	791	16.3	T, N, G, ER, Her2, p53, MIB-1, MAI, AI	All patients: N, T, G, ER, Her-2 In N–: G In N+: N, age, ER, Her2	UV: age. MV All patients: AI, MI, MIB-1, ER, G MV in N- & N+: AI, MI, ER, G.	Breast cancer-specific mortality was measured. When patient FU was truncated at 5 yrs, MI was prognostic factor for N+ and N-
25	Page 2001 [115]	311 no adjuvant therapy.	11.6	High risk group (ER- or T≥3cm) vs. low risk (ER+ and T <2 cm)	T, risk group (high vs. low)	G, MI	Overall survival was measured. MI was only significant when FU was truncated at 5 yrs. Grade was significant prognostic factor for short- and long-term survival.
26	Frkovic-Grazio and Bracko 2001 [48]	270 T1N0M0	12.5	G, Tubular score, MI	Tubular score and MI		Breast cancer-specific survival was measured. This study confirmed the use of Nottingham grading system in their cohort
27	D'Eredita 2001 [49]	402	≥16	T, N, Htyp, G, LVI, NPI	T, N, G	UV: Age, MS, ER, type of surgery MV: LVI & Htyp	Overall survival was measured. NPI gives similar survival prognosis as T, N, G
28	Thomson 2001 [26]	23786	At 10 yrs about 50% patients were alive	Age stratified by SES	Intermediate vs. high SES group corrected for age, ER, N, T, stage	Deprived vs. high SES group corrected for age, ER, N, T, stage	Deprived women have more ER- tumours. ER distribution and treatment method accounted for 20% of disparities in survival
29	Vorgias 2001 [30]	269 stage II	12	NR	T, N, age, ER/PR	MS, therapy	Overall survival was measured

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
30	Vincent-Salomon 2001 [43]	685 T≤3 cm	10.8	G, N, ER, necrosis	N, necrosis, G	UV: Vascular density, LVI, age, PR	Overall survival was measured. Intratumoral vascular density was related to larger tumour size and higher grade
31	Eerola 2001 [77]	Familial BC: 359 Sporadic BC: 59517	NR Diagnosed: 1953–1995 End FU: 1997		Stage, age, period of BC diagnosis, FU time (after 2 and 3 yrs of diagnosis)	BRCA1, BRCA2	5-year relative survival was measured for excess mortality due to BC
32	Kitchen 2001 [35]	9520	12		Tubular BC type vs. other type, by nodal status and chemotherapy		Overall survival was measured. Tubular BC type had better prognosis than other type. This type was more likely to have low G & ER+
33	Kato 2002 [50][a]	422	10	P53, MI, necrosis, T, N, LVI	MI, T, N	UV: AI	Overall survival was measured In MV P53 & MI were independent prognostic factors for N-patients only. P53 was related to MI, AI, necrosis, G, T, N, ER/PR
34	Kato 2002 [54][a]	398	10	BVI, T, N, G, chemotherapy	BVI, T, N, G, chemotherapy	UV: necrosis	Overall survival was measured
35	Costa 2002 [67]	670	11.4	N, T, age, ER/PR	N, T, age	MS, ER/PR	Breast cancer-specific survival was measured. After 5 yrs of FU ER and PR were not independent prognostic factors
36	Menard 2002 [17]	1928	Diagnosed in 1968–69 and 1978–79	Her2, N, T, MS, lymphoid infiltration, PR-	G, T, N, lymphoid infiltration		Overall survival was measured. HER-2 was related to large tumours, higher G, lymphoid infiltration, higher mitotic index, PR-
37	Van de Vijver 2002 [74]	295 age <53, stage I-II	6.7	Gene profile (Good vs. bad prognosis) for all patients, N+, N–	Gene profile, T, N, chemotherapy	VI, G, age, hormonal therapy	Overall survival was measured
38	Van't Veer 2002 [72]	117 age <55	NR				Better classification of patients with high risk of metastasis and in need of chemotherapy

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
39	Hatteville 2002 [21]	3180	15.8		OS <5 year: N, G, recurrence or metastasis OS≥5 yr: G and recurrence or metastasis	Age, T	If patient remains without recurrence or metastasis, effect of prognostic factors decreases over time. With metastases, this effect increases
40	Sotiriou 2003 [73]	99	6.1	Gene profile (luminal 1–3 vs. basal 1–2 & Her2 type)			Luminal-like 1–3 was predominantly ER+. Basal-like 1–2 and Her2 was predominantly ER-
41	Dignam 2003 [83]	3385 N–, ER+	13.8		BMI <18.5 and BMI ≥30 higher total mortality and other deaths.	BMI on deaths after BC events.	Total mortality, death after BC events and other deaths as well as recurrence rate and occurrence of a second cancer was were measured. MV was adjusted for treatment, age, MS, race, T, ER and PR. Reference group was BMI 18.5–24.9.
42	Olivotto 2003 [57]	620 stage IIIB-M1	>20	Supraclavicular BC, Stage IIIB and M1			Overall and breast cancer specific survival were measured. Patients with supraclavicular metastases had significantly better survival than patients with M1. Survival of these patients resembles that of BC stage IIB. (FU for living patients 20 yrs, for all patients 4.5 yrs)
43	Weiss 2003 [32]	905 N+ Chemotherapy+	22.6	N+ (N1–3 vs. N4–9 vs. N >10), also by treatment and follow-up time	N, T, MS	MV: NXT, MSXT, additional vincristine and prednison	Overall survival was measured. N was related to T. MS was related to receptor status
44	Taylor 2003 [16]	54,228	At 10 yrs 65% patients were alive	Period of diagnosis, stage by age, FU time by stage			Relative survival was measured for excess mortality due to BC The longer the survival the better the prognosis. Improvement in relative survival for all patients and all stages since 1972

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
45	Dales 2004 [56]	905 aged 25–81	11.7	In N- : CD105+ vessels. In all pts: CD31, Tie-2/Tek	In all pts: G, CD105 vessels, ER In N–: G, CD105 vessels, PR	In all pts: T, Htyp, CD31, PR, age. In N–: T, CD31 vessels, ER, age	Overall survival was measured. MV: Tie-2/Tek showed significant role for predicting OS in all patients and N- patients
46	Brenner and Hakulinen 2004 [15]	18,578 age <50	NR. Diagnosed: 1953–1999.	Period of diagnosis, stage, stage*period, time after diagnosis			Improvement of prognosis for BC patients younger than 50 over the past decades. Relative survival remains lowered even 40 yrs after diagnosis
47	Robson 2004 [76]	584 Ashkenazi Jewish	116	BRCA1, T, N, ER, age, chemotherapy	BRCA1, T, N, Age	Tamoksifen, BRCA2	Breast cancer-specific survival was measured. No effect of BRCA on non-BC death. BRCA1 only predicted BC death in patients without chemotherapy
48	Chia 2004 [33]	1187 LVI-, N-, Adjuvant systemic therapy-	10.4	T, G	TXG		Overall and breast cancer specific survival were measured. Patients with higher grade and size have greater chance to die from other & those with low risk disease greater chance of death from BC
49	Yoshimoto 2004 [18]	15,416	NR. Diagnosed 1946–2001.	Period of diagnosis			Over the decades, there were less extensive surgery and lymph node examination, less radiotherapy, more chemo- and hormonal therapy
50	Houterman 2004 [116]	527 age ≥40	4.7	Comorbidity, N, Therapy, age≥70, comorbidity*N	In age <70: comorbidity, N In age ≥70: comorbidity, age	In age <70: therapy In pts age≥70: N, therapy	Relative survival was measured for excess mortality due to BC Older patients with comorbidity were not treated differently but had a worse prognosis
51	Schoppmann 2004 [53]	374	22.4	LVI, G, N, Therapy	LVI, G, N	LMVD (Lymphatic Microvessel Density), T, Htyp, ER, age, MS	Overall survival was measured. LVI is related to young premenopausal BC, lower G, N+

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
52	Warwick 2004 [31]	2299	>10	G, N, T, Metastases	G, N, T, Metastases		Breast cancer specific survival was measured. All studied factors predicted long-term survival, but their value decreased over time
53	Berclaz 2004 [82]	6792	14	BMI 25–29, BMI ≥30 lower overall survival	BMI ≥30	BMI 25–29	Overall survival and also disease free survival were measured. Reference group was BMI ≤ 24.9. MV adjusted for ER, T, N, MS, treatment, chemotherapy, hormonal- in combination with chemotherapy
54	Dignam 2005 [84]	4077 N-, ER-	NR		BMI ≥35 and AA had higher overall mortality and non- BC death	BMI and race on death after BC events	Total mortality, death after BC events and other deaths as well as recurrence rate and occurrence of a second cancer were measured. MV was adjusted for treatment, age, MS, race, T, ER and PR Reference group was BMI ≤24.9
55	Holmes 2005 [87]	2987	96 months		Physical activity after diagnosis (MET ≥9) on BC and total mortality		Breast cancer and total mortality were measured. MV corrected for age, interval between diagnosis and physical activity assessment, smoking, BMI, MS, hormone therapy use, age at first birth, parity, energy intake, stage and treatment. MET: metabolic equivalent task hours per week. Patients with BMI ≥25 and more physical activity before diagnosis there was a significant trend for less breast cancer death
56	Robsahm and Tretli 2005 [27]	5042	NR. Diagnosed: 1964–92. End FU: 1992	NR	Location of home, age at first child, physical activity at work	MV corrected for: age, period of diagnosis, birth cohort, educational level	Breast cancer-specific survival was measured. Incidence of BC increases with higher educational level, and case fatality decreases by increasing education level

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
57	Vu-Nishino 2005 [38]	1490 received breast-conserving treatment	13.9			Medullary BC vs. other BC type	Overall survival was measured. Medullary BC type had better prognosis than other type. This type was more likely to have ER+, PR+ & less BRCA1/2 mutation. Medullary type was only a prognostic factor for the first 5 yrs
58	Galper 2005 [63]	2102 stage I-II, 314 with local recurrence (LR)	13.1	NR	No LR treatment, Invasive LR, time (yrs) to local recurrence, age at initial BC diagnosis	T, detection method, number of nodes sampled, ER/PR, histological type, G, LVI, margins	Measure of survival: distant failure, second malignancy, or death Patients with a longer time to recurrence have prolonged survival
59	Voogd 2005 [62]	266 BC with LR	11.2 after LR for living pts	NR	Location of LR, size of LR, skin involvement of LR, N+ for primary tumour		Overall survival was measured. Early detection of local recurrence may improve the treatment outcome
60	Louwman 2005 [13]	8966	Diagnosed 1995–2001. End FU: 2004	2 or more comorbidities, diabetes mellitus and previous cancer	Previous cancer, CVD, DM, cerebrovascular disease, dementia, 2 or more comorbidities, stage, treatment (RT, ST, age)		Overall as well as relative survival was measured for excess mortality due to BC Primary treatment of BC patients with serious comorbidity was less extensive than treatment of those without comorbidity
61	Tammemagi 2005 [14]	906	10	Number of severe comorbidities, race, type of comorbidity	All patients: 3 or more comorbidities adjusted for stage, age, ER, surgery, chemotherapy, radiotherapy		Overall survival was measured. AA had more diabetes and hypertension. After adjustment for these 2 comorbidities disparity disappeared
62	Meunier-Carpentier 2005 [55]	909/918 age: 25–81	11.3	Tie2	–	UV: VEGFR-2, VEGFR-2	Overall survival was measured. VEGFR-1 and Tie2 were reported as independent prognostic factors corrected for T, G, Htyp, in all patients and N-

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
63	Tai 2005 [40]	6184 Inflammatory BC	NR. Diagnosed 1973–1995. End FU: 2000	Period of diagnosis			Breast cancer-specific survival was measured. Prognosis has improved over the decades due to more aggressive therapy
64	Louwman 2005 [71]	492 T1–2 N0	>10 yrs	MAI	OS: age, T BCS: MAI	OS: HTyp, therapy, period of diagnosis. BCS: therapy, period of diagnosis, age, T, Htyp	Overall (OS) as well as relative survival (BCS) was measured for excess mortality due to BC Higher MAI was a significant prognostic factor for N– and N+, but only during the first 10 yrs of FU
65	Arrigada 2006 [8]	2410 T ≤7 cm N1–2	19	T, skin fixation, muscle fixation, G, N, age	Total FU: T, N, G, age <35, age≥55 FU 0–5 yrs: T, N, G, age ≥55 FU 5–10 yrs: N, G, age <35, age ≥ 55 FU 10–15 yrs: N >10, age >55. FU 15–20yrs: age≥65		Overall survival was measured. Long-term effect of prognostic factors vanishing
66	Newman 2006 [29]	90,124. White American: 76,111. AA: 14,013			Age, stage, SES		Meta-analysis. African American is an independent predictor of poor outcome for overall survival and breast cancer specific mortality
67	Menvielle 2006 [24]	407,435 women followed for BC death (N:1408)	Women who died of BC in 1968–96	Level of education by period of diagnosis			Breast cancer death among women with the highest education compared to women with the lowest education in 1968–74 was 0.43; and in 1990–96: 1.17 (NS)
68	Bouchardy 2006 [25]	3920 age <70	NR. Diagnosed in 1980–2000	SES	SES corrected for age, period of diagnosis, marital status, country of birth, Htyp, ER, detection method, stage, sector of care, therapy		Overall survival was measured. Lowest SES had less frequently screen-detected cancers, less stage I, less lobular BC, less BCT, less lymph node dissection

Table 1 continued

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
69	Siegelmann-Danieli 2006 [117]	992, age ≥70	6.9	Being in wheelchair, renal insufficiency, dementia, CHF, cardiac arrhythmia, DM, IHD, osteoporosis, PVD, cerebrovascular disease, COPD, Parkinson's disease, valvular heart disease	In stage 1A-2A: age, CHF, DM, PVD, stage, cardiac arrhythmia, Parkinson's disease, renal insufficiency In stage 2B-4: G, stage, N, wheelchair-bound, renal insufficiency, COPD, age, DM	Systemic therapy	Overall survival was measured. CHF: Cardiac Heart Failure. DM: Diabetes Mellitus. IHD: Ischemic Heart Disease. PVD: Peripheral Heart Disease. COPD: Chronic Obstructive Pulmonary Disease. Role of comorbidity varies by age
70	Pritchard 2006 [68]	639 premenopausal N+	10	Her2 amplification	Her2 corrected for age, N, ER, type of surgery		Overall survival was measured. Those with amplified Her2 have improved survival with CEF
71	Lee 2006 [52]	(A) Adjuvant therapy – : 990. (B) Adjuvant treatment +: 1765	Group A: 13 Group B: 6.8.	LVI	Group A: T, G, LVI, Htyp Group B: T, G, LVI, chemotherapy, hormonal therapy	B: ER, age, Htyp	Breast cancer-specific survival was measured For patients without adjuvant treatment, role of G in survival was higher in the first 5 yrs. Role of Htyp was not significant for the first 5 yrs of FU

[a] indicates the overlapping patients used by the same author to answer another research question; yrs: years; UV: Univariate analysis. MV: Multivariate analysis. MS: Menopausal Status; T: Tumour size; N: Nodal involvement; Htyp: Histological type; MI: Mitotic Index; G: Grade; PR: Progesterone Receptor status; ER: Oestrogen Receptor status; PCNA: proliferating cell nuclear antigen; mos: months; NR: Not Reported; AA: African American; age: is in year and indicate age at primary breast cancer unless otherwise state; NPI: Nottingham Prognostic Index; LVI: Lymphovascular Invasion; (Prognostic factor)*(Prognostic factor): interaction between two factors; BMI: Body Mass Index; AMC: Average Microvessel Count; MAI: Mitotic Activity Index; AI: Apoptosis Index; FU: Follow-up; SES: Socioeconomic Status; BVI: Blood vessel Invasion; LMVD: Lymphatic Microvessel Density; LR: local recurrence; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; RT: radiotherapy; ST: Systemic therapy; VEGFR: Vascular Endothelial Growth Factor Receptor; OS: Overall survival; BCS: Breast Cancer Specific Survival; NS: not significant; CHF: Cardiac Heart Failure; IHD: Ischemic Heart Disease. PVD: Peripheral Heart Disease. COPD: Chronic Obstructive Pulmonary. CEF: cyclophosphamide, epirubicin and fluorouracil

Table 2 Selected prognostic factors for long-term overall mortality of breast cancer (BC) patients

Patient groups based	Hazard ratio (HR) for overall follow-up or survival probability (S) 10 years after diagnosis	Morphology based	Hazard ratio (HR) for overall follow-up or survival probability (S) 10 years after diagnosis	Molecular based	Hazard ratio (HR) for overall follow-up or survival probability (S) 10 years after diagnosis
Age at diagnosis [8]	HR:	Lymph node status [31]	HR:	HER2[69]	HR:
<35 vs. 35–44	1.4 (*P*: 0.07)	N≥1 vs. N0	2.4 (1.9–2.9)	>500 vs. ≤500	1.82 (1.1–2.9)
45–54 vs. 35–44	1.1 (ns)	Metastases vs. N0	22.73 (16.1–32.2)		Only in node-positive
55–64 vs. 35–44	2.0 (*P*: 0.000)				
65–75 vs. 35–44	2.5 (*P*: 0.000)				
Period of diagnosis [16]	Relative survival[b]:	Tumour size (mm)[31]	HR:	Cell proliferation index	HR:
1972–1976	59%	T10–14 vs. T1–9	1.2 (0.8–1.9)	(MAI)	
1977–1986	64%	T15–19 vs. T1–9	1.7 (1.1–2.6)	>10 vs. ≤10 [10]	1.02 (1.00–1.03)
1987–1991	70%	T20–29 vs. T1–9	2.5 (1.6–3.9)		Only in node-positive patients
		T30–49 vs. T1–9	3.8 (2.4–6.0)		
		T≥50 vs. T1–9	4.6 (2.9–7.6)		
Time after diagnosis [16]	Relative survival:	Tumour grade [44]	HR:	Gene expression profile [74]	S:
0 vs. 5 yrs after diagnosis		II vs. I	2.5 (1.0–6.1)		55% vs. 95%
Regional BC	79% vs. 84%	III vs. I	5.7(2.6–12.4)	Poor vs. good signature[f]	
Locally advanced BC	53% vs. 68%				
Socioeconomic status [26]	HR:	Tumour type[34]	S:	ER/PR status [30]	HR:
Intermediate vs. affluent	1.2 (1.0–1.4)	Poor vs. excellent [d,e]	<50% vs. >80%	Positive vs. negative	0.38 (0.02–1.06)
Deprived vs. affluent	1.2 (0.99–1.53)				
Lifestyle	HR:				
Body Mass Index					
<21 vs. 29+ kg/m^2	1.4 (0.97–2.00) [85] [c]				
Physical activity					
< 3 vs. 23.9 MET-h/wk[a]	0.56 (0.4–0.8) [87]				

HR: Hazard ratio calculated within multivariate analysis of breast cancer patients followed for a median/mean of 10 years or longer [a] Metabolic equivalent task hours per week; [b] Estimates taken from graph; [c] Higher alcohol intake no significant effect on mortality. Significant trend of higher mortality for lowest compared to highest quintiles of fibre, lutein and zeaxanthin, calcium & protein intake; [d] Becomes larger as numbers of involved lymph nodes increases [8]; [e] Excellent prognosis: tubular, invasive cribriform, mucinous, tubulolobular. Poor prognosis: mixed lobular, solid lobular, ductal and mixed ductal lobular; [f] unadjusted estimates

other prognostic factors in determining survival for long-term survivors still needs to be determined.

The role of early detection

Increased awareness among women and improvement in diagnostic procedures have enabled earlier and better detection of BC. Trials on population screening have reported 21–29% reduction in BC mortality for women invited for screening within 14–16 years of follow-up [19, 97]. Screening identified tumours at an early stage consequently, survival improved [98, 99]. Screening also identified patients with slowly growing tumours who might receive unnecessarily aggressive cancer treatment. Thus, Joensuu et al. [100] examined recurrence rates among patients detected by screening compared to those detected outside screening. After adjusting for tumour aggressiveness (tumour size, nodal status, grade, age, treatment, PR status, HER-2), hence eliminating bias towards detection of indolent cancers (length bias), the benefit of screening for the prognosis for BC patients remained evident.[100] This suggests that other factors explain the indolent behaviour of BC detected by screening. Hence, until this factor is established, detection mode should probably be considered as a prognostic factor and thus be taken into account in patient management.

The role of treatment

Improvement in BC treatment has undoubtedly also increased the long-term survival of BC patients [101], as reflected by the improved overall survival across all BC stages [16]. Using historical data from population-based studies in periods when effective treatment was not available, it was estimated that without treatment only 4% of BC patients would survive 10 years or longer [102]. BC treatment guidelines have been modified continuously in the last 28 years, tailored to most of the prognosticators mentioned earlier [51]. Effectiveness of various treatment modalities has been summarized by others who conclude that radiation, chemotherapy and hormonal therapy may reduce long-term mortality by up to 57% [66, 103–105]. Emerging new therapeutic approaches using a monoclonal antibody directed against HER-2 have yielded improved short-term survival for advanced stage [106] as well as operable BC patients [107]. Quality of treatment as indicated by loco-regional failure [108], surgeon workload [109] or hospital volume [110], may affect survival although its role on long-term survival still needs confirmation. In conclusion, on the one hand we have observed a shift in stage towards less aggressive cancers; on the other hand, better and more (systemic) treatment has become available, leading to improved survival for BC patients.

Conclusion

The prognosis of BC has become relatively good, with current 10-year relative survival about 70% in most western populations [16, 111], especially if up-to-date statistical method such as the period analyses is used [111] (Table 1). Even better, the longer patients survive their BC the higher their survival chance [16]. Our review shows conventional prognostic factors of survival, such as tumour size, lymph node status and grade, remain the most important determinants of 10-year survival for BC patients (Table 2). Most studies agreed on the value of MAI and LVI for prediction of long-term survival. The influence of host factors including age, race/ethnicity or socio-economic factors and tumour-related factors such as histological type and angiogenesis diminishes after correction for other factors. For most recent markers such as Her2, gene profiling, p53 mutation and uPA level longer follow-up is needed. Recurrence, metastases and a second cancer double the burden of disease thus increase risk of mortality. Similarly, co-occurrence with other diseases is in no doubt decrease survival.

Healthier lifestyle generally increases long-term survival. Modifiable risk factors (such as alcohol consumption and obesity) not only affect incidence but also tumour' clinical behaviour and thus survival.

Although a lot is known about the prognosis for BC patients, effect of traditional prognostic factors appears to attenuate over time, leaving room for studies on the role of other and newer factors for long-term survival.

References

1. Parkin DM, Bray F, Ferlay J et al (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Sant M, Aareleid T, Berrino F et al (2003) EUROCARE-3: survival of cancer patients diagnosed 1990–94-results and commentary. Ann Oncol 14(Suppl 5):v61–118
3. Botha JL, Bray F, Sankila R et al (2003) Breast cancer incidence and mortality trends in 16 European countries. Eur J Cancer 39:1718–1729
4. ACS: Cancer facts and figures 2005. Atlanta, 2005
5. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV et al (2005) Van meten naar weten. 50 jaar kankerregistratie. Integraal Kankercentrum Zuid (IKZ), Eindhoven, 104 pp
6. Kroman N, Jensen MB, Wohlfahrt J et al (2000) Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ 320:474–478
7. Aebi S, Gelber S, Castiglione-Gertsch M et al (2000) Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? Lancet 355:1869–1874
8. Arriagada R, Le MG, Dunant A et al (2006) Twenty-five years of follow-up in patients with operable breast carcinoma: correlation between clinicopathologic factors and the risk of death in each 5-year period. Cancer 106:743–750
9. Fisher ER, Anderson S, Tan-Chiu E et al (2001) Fifteen-year prognostic discriminants for invasive breast carcinoma: National

Surgical Adjuvant Breast and Bowel Project Protocol-06. Cancer 91:1679–1687
10. Pietilainen T, Lipponen P, Aaltomaa S et al (1995) Expression of p53 protein has no independent prognostic value in breast cancer. J Pathol 177:225–232
11. Kollias J, Elston CW, Ellis IO et al (1997) Early-onset breast cancer—histopathological and prognostic considerations. Br J Cancer 75:1318–1323
12. West DW, Satariano WA, Ragland DR et al (1996) Comorbidity and breast cancer survival: a comparison between black and white women. Ann Epidemiol 6:413–419
13. Louwman WJ, Janssen-Heijnen ML, Houterman S et al (2005) Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 41:779–785
14. Tammemagi CM, Nerenz D, Neslund-Dudas C et al (2005) Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 294:1765–1772
15. Brenner H, Hakulinen T (2004) Are patients diagnosed with breast cancer before age 50 years ever cured? J Clin Oncol 22:432–438
16. Taylor R, Davis P, Boyages J (2003) Long-term survival of women with breast cancer in New South Wales. Eur J Cancer 39:215–222
17. Menard S, Balsari A, Casalini P et al (2002) HER-2-positive breast carcinomas as a particular subset with peculiar clinical behaviors. Clin Cancer Res 8:520–525
18. Yoshimoto M, Tada K, Hori H et al (2004) Improvement in the prognosis of Japanese breast cancer patients from 1946 to 2001–an institutional review. Jpn J Clin Oncol 34:457–462
19. Nystrom L, Andersson I, Bjurstam N et al (2002) Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 359:909–919
20. Otto SJ, Fracheboud J, Looman CW et al (2003) Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 361:1411–1417
21. Hatteville L, Mahe C, Hill C (2002) Prediction of the long-term survival in breast cancer patients according to the present oncological status. Stat Med 21:2345–2354
22. Brenner H, Gefeller O, Hakulinen T (2004) Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. Eur J Cancer 40:326–335
23. Hooning MJ, Aleman BM, van Rosmalen AJ et al (2006) Cause-specific mortality in long-term survivors of breast cancer: a 25-year follow-up study. Int J Radiat Oncol Biol Phys 64:1081–1091
24. Menvielle G, Leclerc A, Chastang JF et al (2006) Social inequalities in breast cancer mortality among French women: disappearing educational disparities from 1968 to 1996. Br J Cancer 94:152–155
25. Bouchardy C, Verkooijen HM, Fioretta G (2006) Social class is an important and independent prognostic factor of breast cancer mortality. Int J Cancer 119(5):1145–1151
26. Thomson CS, Hole DJ, Twelves CJ et al (2001) Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. J Epidemiol Community Health 55:308–315
27. Robsahm TE, Tretli S (2005) Weak associations between sociodemographic factors and breast cancer: possible effects of early detection. Eur J Cancer Prev 14:7–12
28. Wojcik BE, Spinks MK, Optenberg SA (1998) Breast carcinoma survival analysis for African American and white women in an equal-access health care system. Cancer 82:1310–1218
29. Newman LA, Griffith KA, Jatoi I et al (2006) Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. J Clin Oncol 24:1342–1349
30. Vorgias G, Koukouras D, Paleogianni V et al (2001) Prognostic significance of factors affecting disease free interval and overall survival for Stage II breast cancer in Greece. A multivariate cohort study. Eur J Obstet Gynecol Reprod Biol 95:100–104
31. Warwick J, Tabar L, Vitak B et al (2004) Time-dependent effects on survival in breast carcinoma: results of 20 years of follow-up from the Swedish Two-County Study. Cancer 100:1331–1336
32. Weiss RB, Woolf SH, Demakos E et al (2003) Natural history of more than 20 years of node-positive primary breast carcinoma treated with cyclophosphamide, methotrexate, and fluorouracil-based adjuvant chemotherapy: a study by the Cancer and Leukemia Group B. J Clin Oncol 21:1825–1835
33. Chia SK, Speers CH, Bryce CJ et al (2004) Ten-year outcomes in a population-based cohort of node-negative, lymphatic, and vascular invasion-negative early breast cancers without adjuvant systemic therapies. J Clin Oncol 22:1630–1637
34. Galea MH, Blamey RW, Elston CE et al (1992) The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Res Treat 22:207–219
35. Kitchen PR, Smith TH, Henderson MA et al (2001) Tubular carcinoma of the breast: prognosis and response to adjuvant systemic therapy. ANZ J Surg 71:27–31
36. Northridge ME, Rhoads GG, Wartenberg D et al (1997) The importance of histologic type on breast cancer survival. J Clin Epidemiol 50:283–290
37. Reed W, Hannisdal E, Boehler PJ et al (2000) The prognostic value of p53 and c-erb B-2 immunostaining is overrated for patients with lymph node negative breast carcinoma: a multivariate analysis of prognostic factors in 613 patients with a follow-up of 14–30 years. Cancer 88:804–813
38. Vu-Nishino H, Tavassoli FA, Ahrens WA et al (2005) Clinicopathologic features and long-term outcome of patients with medullary breast carcinoma managed with breast-conserving therapy (BCT). Int J Radiat Oncol Biol Phys 62:1040–1047
39. Gamel JW, Meyer JS, Feuer E et al (1996) The impact of stage and histology on the long-term clinical course of 163,808 patients with breast carcinoma. Cancer 77:1459–1464
40. Tai P, Yu E, Shiels R et al (2005) Short- and long-term cause-specific survival of patients with inflammatory breast cancer. BMC Cancer 5:137
41. Harris JR, Lippman ME, Morrow M et al (2004) Diseases of the breast 3rd edn. Philadelphia, Lippincott Williams & Wilkins
42. Gilchrist KW, Kalish L, Gould VE et al (1985) Interobserver reproducibility of histopathological features in stage II breast cancer. An ECOG study. Breast Cancer Res Treat 5:3–10
43. Vincent-Salomon A, Carton M, Zafrani B et al (2001) Long term outcome of small size invasive breast carcinomas independent from angiogenesis in a series of 685 cases. Cancer 92:249–256
44. Kato T, Kameoka S, Kimura T et al (2001) Angiogenesis as a predictor of long-term survival for 377 Japanese patients with breast cancer. Breast Cancer Res Treat 70:65–74
45. Tabar L, Duffy SW, Vitak B et al (1999) The natural history of breast carcinoma: what have we learned from screening? Cancer 86:449–462
46. Kollias J, Murphy CA, Elston CW et al (1999) The prognosis of small primary breast cancers. Eur J Cancer 35:908–912
47. Pinder SE, Murray S, Ellis IO et al (1998) The importance of the histologic grade of invasive breast carcinoma and response to chemotherapy. Cancer 83:1529–1539

48. Frkovic-Grazio S, Bracko M (2002) Long term prognostic value of Nottingham histological grade and its components in early (pT1N0M0) breast carcinoma. J Clin Pathol 55:88–92
49. D'Eredita G, Giardina C, Martellotta M et al (2001) Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution. Eur J Cancer 37:591–596
50. Kato T, Kameoka S, Kimura T et al (2002) p53, mitosis, apoptosis and necrosis as prognostic indicators of long-term survival in breast cancer. Anticancer Res 22:1105–1112
51. Goldhirsch A, Glick JH, Gelber RD et al (2005) Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 16:1569–1583
52. Lee AH, Pinder SE, Macmillan RD et al (2006) Prognostic value of lymphovascular invasion in women with lymph node negative invasive breast carcinoma. Eur J Cancer 42:357–362
53. Schoppmann SF, Bayer G, Aumayr K et al (2004) Prognostic value of lymphangiogenesis and lymphovascular invasion in invasive breast cancer. Ann Surg 240:306–312
54. Kato T, Kameoka S, Kimura T et al (2002) Blood vessel invasion as a predictor of long-term survival for Japanese patients with breast cancer. Breast Cancer Res Treat 73:1–12
55. Meunier-Carpentier S, Dales JP, Djemli A et al (2005) Comparison of the prognosis indication of VEGFR-1 and VEGFR-2 and Tie2 receptor expression in breast carcinoma. Int J Oncol 26:977–984
56. . Dales JP, Garcia S, Carpentier S et al (2004) Long-term prognostic significance of neoangiogenesis in breast carcinomas: comparison of Tie-2/Tek, CD105, and CD31 immunocytochemical expression. Hum Pathol 35:176–183
57. Olivotto IA, Chua B, Allan SJ et al (2003) Long-term survival of patients with supraclavicular metastases at diagnosis of breast cancer. J Clin Oncol 21:851–854
58. Nomura Y, Tsutsui S, Murakami S et al (1999) Prognostic impact of second cancer on the survival of early breast cancer patients. Int J Oncol 14:1103–1109
59. Raymond JS, Hogue CJ (2006) Multiple primary tumours in women following breast cancer, 1973–2000. Br J Cancer 94:1745–1750
60. Kollias J, Ellis IO, Elston CW et al (2001) Prognostic significance of synchronous and metachronous bilateral breast cancer. World J Surg 25:1117–1124
61. Wapnir IL, Anderson SJ, Mamounas EP et al (2006) Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24:2028–2037
62. Voogd AC, van Oost FJ, Rutgers EJ et al (2005) Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. Eur J Cancer 41:2637–2344
63. Galper S, Blood E, Gelman R et al (2005) Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. Int J Radiat Oncol Biol Phys 61:348–357
64. Habel LA, Shak S, Jacobs MK et al (2006) A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Breast Cancer Res 8:R25
65. Obedian E, Fischer DB, Haffty BG (2000) Second malignancies after treatment of early-stage breast cancer: lumpectomy and radiation therapy versus mastectomy. J Clin Oncol 18: 2406–2412
66. Early Breast Cancer Trialists' Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717
67. Costa SD, Lange S, Klinga K et al (2002) Factors influencing the prognostic role of oestrogen and progesterone receptor levels in breast cancer—results of the analysis of 670 patients with 11 years of follow-up. Eur J Cancer 38:1329–1334
68. Pritchard KI, Shepherd LE, O'Malley FP et al (2006) HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 354:2103–2111
69. Ferrero-Pous M, Hacene K, Bouchet C et al (2000) Relationship between c-erbB-2 and other tumor characteristics in breast cancer prognosis. Clin Cancer Res 6:4745–4754
70. Haerslev T, Jacobsen GK, Zedeler K (1995) Proliferating cell nuclear antigen (PCNA) and c-erbB-2 oncoprotein in breast carcinoma with correlations to histopathological parameters and prognosis. Oncol Rep 2:99–105
71. Louwman WJ, van Beek MW, Schapers RF et al (2005) Long-term survival of T1 and T2 lymph node-negative breast cancer patients according to mitotic activity index: a population-based study. Int J Cancer 118(9):2310–2314
72. van 't Veer LJ, Dai H, van de Vijver MJ et al (2002) Gene expression profiling predicts clinical outcome of breast cancer. Nature 415:530–536
73. Sotiriou C, Neo SY, McShane LM et al (2003) Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci USA 100:10393–10398
74. van de Vijver MJ, He YD, van't Veer LJ et al (2002) A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347:1999–2009
75. Miki Y, Swensen J, Shattuck-Eidens D et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71
76. Robson ME, Chappuis PO, Satagopan J et al (2004) A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 6:R8–R17
77. Eerola H, Vahteristo P, Sarantaus L et al (2001) Survival of breast cancer patients in BRCA1, BRCA2, and non-BRCA1/2 breast cancer families: a relative survival analysis from Finland. Int J Cancer 93:368–372
78. Ferrero JM, Ramaioli A, Formento JL et al (2000) P53 determination alongside classical prognostic factors in node-negative breast cancer: an evaluation at more than 10-year follow-up. Ann Oncol 11:393–397
79. Haerslev T, Jacobsen GK (1995) An immunohistochemical study of p53 with correlations to histopathological parameters, c-erbB-2, proliferating cell nuclear antigen, and prognosis. Hum Pathol 26:295–301
80. Mirza AN, Mirza NQ, Vlastos G et al (2002) Prognostic factors in node-negative breast cancer: a review of studies with sample size more than 200 and follow-up more than 5 years. Ann Surg 235:10–26
81. Fitzgibbons PL, Page DL, Weaver D et al (2000) Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 124:966–78
82. Berclaz G, Li S, Price KN et al (2004) Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. Ann Oncol 15:875–884
83. Dignam JJ, Wieand K, Johnson KA et al (2003) Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 95:1467–1476
84. Dignam JJ, Wieand K, Johnson KA et al (2006) Effects of obesity and race on prognosis in lymph node-negative, estrogen

receptor-negative breast cancer. Breast Cancer Res Treat 97(3):245–254
85. Holmes MD, Stampfer MJ, Colditz GA et al (1999) Dietary factors and the survival of women with breast carcinoma. Cancer 86:826–835
86. Byers T, Sedjo RL (2006) A weight loss trial for breast cancer recurrence: pre-menopausal, post-menopausal, both, or neither? Cancer Causes Control 17:1–3
87. Holmes MD, Chen WY, Feskanich D et al (2005) Physical activity and survival after breast cancer diagnosis. JAMA 293:2479–2486
88. Brown JK, Byers T, Doyle C et al (2003) Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 53:268–291
89. Kroenke CH, Fung TT, Hu FB et al (2005) Dietary patterns and survival after breast cancer diagnosis. J Clin Oncol 23:9295–9303
90. Colditz GA (2005) Estrogen, estrogen plus progestin therapy, and risk of breast cancer. Clin Cancer Res 11:909s–917s
91. Garcia-Closas M, Brinton LA, Lissowska J et al (2006) Established breast cancer risk factors by clinically important tumour characteristics. Br J Cancer 95:123–129
92. Suzuki R, Rylander-Rudqvist T, Ye W et al (2006) Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: a prospective cohort study. Int J Cancer 119:1683–1689
93. Suzuki R, Ye W, Rylander-Rudqvist T et al (2005) Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst 97:1601–1608
94. Takeuchi H, Baba H, Kano T et al (2005) The time-related changes of the importance of prognostic factors in breast cancer. A sequential multivariate analysis of 1423 Japanese patients. Breast Cancer Res Treat 94:273–278
95. Zahl PH, Tretli S (1997) Long-term survival of breast cancer in Norway by age and clinical stage. Stat Med 16:1435–1449
96. Liu S, Edgerton SM, Moore DH 2nd et al (2001) Measures of cell turnover (proliferation and apoptosis) and their association with survival in breast cancer. Clin Cancer Res 7:1716–1723
97. Alexander FE, Anderson TJ, Brown HK et al (1999) 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. Lancet 353:1903–1908
98. Tabar L, Yen MF, Vitak B et al (2003) Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet 361:1405–1410
99. Shen Y, Yang Y, Inoue LY et al (2005) Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. J Natl Cancer Inst 97:1195–1203
100. Joensuu H, Lehtimaki T, Holli K et al (2004) Risk for distant recurrence of breast cancer detected by mammography screening or other methods. JAMA 292:1064–1073
101. Peto R, Boreham J, Clarke M et al (2000) UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. Lancet 355:1822
102. Johnstone PA, Norton MS, Riffenburgh RH (2000) Survival of patients with untreated breast cancer. J Surg Oncol 73:273–277
103. Fisher B, Jeong JH, Bryant J et al (2004) Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet 364:858–868
104. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366:2087–2106
105. Fisher B, Jeong JH, Anderson S et al (2004) Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials. J Natl Cancer Inst 96:1823–1831
106. Hurley J, Doliny P, Reis I et al (2006) Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol 24:1831–1838
107. Romond EH, Perez EA, Bryant J et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673–1684
108. Ernst MF, Voogd AC, Coebergh JW et al (2004) Using loco-regional recurrence as an indicator of the quality of breast cancer treatment. Eur J Cancer 40:487–493
109. Stefoski Mikeljevic J, Haward RA, Johnston C et al (2003) Surgeon workload and survival from breast cancer. Br J Cancer 89:487–491
110. Simunovic M, Rempel E, Theriault ME et al (2006) Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. Can J Surg 49:251–258
111. Houterman S, Janssen-Heijnen ML, van de Poll-Franse LV et al (2006) Higher long-term cancer survival rates in southeastern Netherlands using up-to-date period analysis. Ann Oncol 17(4):709–712
112. Haerslev T, Jacobsen GK, Zedeler K (1996) Correlation of growth fraction by Ki-67 and proliferating cell nuclear antigen (PCNA) immunohistochemistry with histopathological parameters and prognosis in primary breast carcinomas. Breast Cancer Res Treat 37:101–113
113. Gaffney DK, Brohet RM, Lewis CM et al (1998) Response to radiation therapy and prognosis in breast cancer patients with BRCA1 and BRCA2 mutations. Radiother Oncol 47:129–136
114. Mansi JL, Gogas H, Bliss JM et al (1999) Outcome of primary-breast-cancer patients with micrometastases: a long-term follow-up study. Lancet 354:197–202
115. Page DL, Gray R, Allred DC et al (2001) Prediction of node-negative breast cancer outcome by histologic grading and S-phase analysis by flow cytometry: an Eastern Cooperative Oncology Group Study (2192). Am J Clin Oncol 24:10–18
116. Houterman S, Janssen-Heijnen ML, Verheij CD et al (2004) Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer 90:2332–2337
117. Siegelmann-Danieli N, Khandelwal V, Wood GC et al (2006) Breast cancer in elderly women: outcome as affected by age, tumor features, comorbidities, and treatment approach. Clin Breast Cancer 7:59–66