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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

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
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
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 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.
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.

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 its 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 to 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                               | PR was only an independent factor in N-positive pts. Her2 & PCNA were related to more positive N, higher G, ER-/PR-negative. 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) | Overall survival was measured. 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. |
| 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, LVI | 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] | 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 analysis significant | Multivariate 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, age 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 | |
| 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] | 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  | Fkovic-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 group corrected for age, ER, N, T, stage | 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 |
| 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 | 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. Breast cancer-specific survival was measured. After 5 yrs of FU ER and PR were not independent prognostic factors |
| 35  | Costa 2002 [67] | 670 | 11.4 | N, T, age, ER/PR | N, T, age | MS, ER/PR | |
| 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. Better classification of patients with high risk of metastasis and in need of chemotherapy |
| 38  | Van’t Veer 2002 [72] | 117 age <55 | NR | | | | |
| 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 | Age, T | OS 5 yr: G and recurrence or metastasis | 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 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 IIIB. (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 |
| 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, Hyp, 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 | | 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 | | 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, Hyp, ER, age, MS | Overall survival was measured. LVI is related to young premenopausal BC, lower G, N+ |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 | OS: HTyp, therapy, period of diagnosis, BCS: MAI | 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 | | | | | 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 |
| No. | Author, year | No. of patients | Mean/median follow-up (yrs) | Univariate analysis significant | Multivariate 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 | 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 −: Group A: 13 | LVI | | | | 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 |
|     |               | (B) Adjuvant treatment +: 1765 | Group B: 6.8. | | | | |

*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; NPE: 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; BVE: 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 Disease. 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]** |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| <35 vs. 35–44        | 1.4 (P: 0.07)                                                                                  | Lymph node status [31] | 2.4 (1.9–2.9)                                                                                  | HER2 [69] | >500 vs. ≤500                                                                                  |
| 45–54 vs. 35–44       | 1.1 (ns)                                                                                      | N≥1 vs. N0       |                                                                                              | HR:             |                                                                                              |
| 55–64 vs. 35–44       | 2.0 (P: 0.000)                                                                                 | Metastases vs. N0 | 22.73 (16.1–32.2)                                                                             | HR:             |                                                                                              |
| 65–75 vs. 35–44       | 2.5 (P: 0.000)                                                                                 |                  |                                                                                              | HR:             | Only in node-positive                                                                           |
| **Period of diagnosis [16]** |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| 1972–1976             | 59%                                                                                           | Tumour size (mm)[31] | 1.2 (0.8–1.9)                                                                                  | Cell proliferation index (MAI) | >10 vs. ≤10 [10]                                                                                  |
| 1977–1986             | 64%                                                                                           | T10–14 vs. T1–9  |                                                                                              | HR:             | Only in node-positive                                                                           |
| 1987–1991             | 70%                                                                                           | T15–19 vs. T1–9  |                                                                                              | HR:             | Only in node-positive                                                                           |
| **Time after diagnosis [16]** |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| 0 vs. 5 yrs after diagnosis |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| Regional BC           | 79% vs. 84%                                                                                   | T20–29 vs. T1–9 | 2.5 (1.6–3.9)                                                                                  | HR:             |                                                                                              |
| Locally advanced BC   | 53% vs. 68%                                                                                   | T30–49 vs. T1–9 | 3.8 (2.4–6.0)                                                                                  | HR:             |                                                                                              |
| **Socioeconomic status [26]** |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| Intermediate vs. affluent | 1.2 (1.0–1.4)                                                                               | T≥50 vs. T1–9   | 4.6 (2.9–7.6)                                                                                  | S:              |                                                                                              |
| Deprived vs. affluent  | 1.2 (0.99–1.53)                                                                               |                  |                                                                                              | HR:             |                                                                                              |
| **Lifestyle**         |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| Body Mass Index       |                                                                                               |                  |                                                                                              |                  |                                                                                              |
| <21 vs. 29+ kg/m²     | 1.4 (0.97–2.00)                                                                               |                  |                                                                                              | S:              |                                                                                              |
| Physical activity     |                                                                                               |                  |                                                                                              | HR:             |                                                                                              |
| < 3 vs. 23.9 MET-h/wk | 0.56 (0.4–0.8)                                                                                |                  |                                                                                              | HR:             |                                                                                              |

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; 0.07. 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. 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.

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