18 Breast Carcinoma

H.B. Burke, R.V.P. Hutter, and D.E. Henson

There has been a proliferation of prognostic factors in breast cancer. Currently there are at least 76 putative breast cancer prognostic factors reported in humans. In this chapter the literature for 37 factors is reviewed. The factors that are supported in the literature are not necessarily the final prognostic factors for breast cancer. They deserve further study in an integrative model. The prognostic factors are presented in three tables, each representing a level of analysis, i.e., epidemiologic, anatomic–cellular, and molecular–genetic.

Before proceeding it is necessary to mention factors that are not reviewed. Treatment (physician, therapeutic modality, compliance, etc.) is a large domain that cannot be adequately addressed in a chapter that is primarily a compilation of prognostic factors. Psychological prognostic factors, e.g., adverse life events [2], have not been well supported in the literature, probably because of the poor sensitivity of the assessment instruments. Performance status has not been shown to be a powerful prognostic factor [70]. Quality of life during chemotherapy may be a predictor of overall survival [14].

The following serum biochemical markers are not discussed because they have been recently reviewed elsewhere [60,68]: the adenocarcinoma marker carcinoembryonic antigen (CEA), the breast mucin markers CA 15–3, CA 549, CA M26, CA M29, mucin-like carcinoma-associated antigen (MCA), mammary serum antigen (MSA), cancer-associated serum antigen (CASA), the reaction products hydroxyproline, ferritin, and isoferritin (p43), tumor-associated trypsin inhibitor (TATI), C-reactive protein (CRP), orosomucoid, erythrocyte sedimentation rate (ESR), and the proliferation marker tissue polypeptide antigen (TPA). Many of these markers are a nonspecific host response to the tissue damage caused by the cancer. Their utility has not been well studied, but the available research suggests that most lack adequate sensitivity and specificity for outcome prediction. With sequential testing, some may be useful for the quantification of tumor burden, the monitoring of disease, and the determination of therapeutic effect.

Other prognostic factors are not discussed because each has only a few reports in the literature or are from one research group. These include vitamin D, urokinase-type plasminogen activator, tetranectin, TRPM-2, multicentricity, tumor necrosis factor alpha (not the same as histologic tumor necrosis), tubule formation, laminin, type 2 carbohydrate, haptoglobin-related protein, natural killer cells, chromosome 11q13, alterations in chromosome 1, nuclear volume,

Table 1. Epidemiologic prognostic factors

Name	Literature support	Properties	References
Age	+	Age is usually a significant predictor because of its small measurement variability. A recent study suggests worse prognosis in premenopausal women	47, 49
Co-morbidity	+	Worse outcome regardless of early diagnosis	52
Dietary fat	0	Relationship between dietary fat and outcome is unclear, research is in progress to clarify relationship	29
Obesity	+	Poor prognosis in women receiving adjuvant chemotherapy	3
Race	+	African-Americans have lower survival rates, possibly due to economic status	1, 59

+, Well supported; 0, equivocal support.

tumor-infiltrating lymphocytes, glutathione level, Glut-1 glucose transporter, cyclic adenosine monophosphate (cAMP)-binding proteins, Bcl-2 protein, and matrix metalloproteinase-2. Epidemiologic prognostic factors are listed in Table 1, anatomic and cellular factors in Table 2, while molecular-genetic prognostic factors are shown in Table 3.

Discussion

Many researchers are actively engaged in the search for new prognostic factors for breast cancer patients. Their research efforts have the potential to dramatically increase predictive accuracy; however, the proliferation of putative prognostic factors has given rise to two problems, the poor reproducibility of results (interstudy variability) and the inability of prognostic factors to be integrated into a predictive system.

There are a number of reasons for the interstudy variability. They include: sampling error, the use of different laboratory assays for a prognostic factor, varying levels of laboratory skill and quality control, different cut-off points for the definition of a positive finding, the enrollment of small populations and special patient subgroups, capturing too few outcome events, providing limited follow-up, employing different end points, using different statistical models, and testing for independence with ad hoc groups of prognostic factors.

A review of the significance, independence, and clinical usefulness [8] of a putative prognostic factor requires, for a specific end point, a description of the sampling method, a description of the assay, assessment of intraobserver, interobserver, and interlaboratory variability, a description of the cut-off point criteria and whether the cut-off point was selected before the data were analyzed, a listing of the subject enrollment criteria, subject characteristics, the number of subjects and outcome events, the therapeutic intervention(s), the duration of

Table 2. Anatomic and cellular prognostic factors

Name	Literature support	Properties	References
Tumor size, extent (T)	+	Pathologic more reliable than clinical	47
Regional lymph node involvement (N)	+	Pathologic more reliable than clinical	9
Metastasis (M)	+	Radiographic tests acceptable	31
Histology: Type	+	Most breast cancer is ductal	19
Grade	+	Problems with uniformity of criteria	7, 21, 27
Chromatin	+	Nuclear morphology	33
Tumor necrosis	+	Cell degeneration and death	20
Mitotic counts	+	Cell activity, fixative problems, only M-phase cells	13, 30
DNA ploidy	0	Conflicting results	36
Thymidine labeling index	+	Cell proliferation, thymidine a DNA precursor, thymidine analogue 5-bromodeoxyuridine also used, predicts recurrence	39, 41, 56
S-phase; flow cytometry	+	Cell proliferation, no standardized cut-off point	36
Ki-67 antibody	+	Recognizes nuclear antigen expressed only in proliferating cells	64, 67
Proliferating cell nuclear antigen (PCNA)	0	Cell cycle-dependent protein that accumulates in the nucleus of replicating cells during S-phase, conflicting results	6
Angiogenesis[a]	+	Related to tumor angiogenesis factors	66
Peritumoral lymphatic vessel invasion	+	Significant for relapse-free survival but not overall survival	19

+, Well supported; 0, equivocal support.

[a] Factor VIII-related antigen and CD 31 are vascular detection techniques for quantifying tumor angiogenesis. Basic fibroblast growth factor is an angiogenic peptide and can be measured in the urine [40]. The degree of correlation between vascular antigens and angiogenic peptide in tumor angiogenesis is not known.

follow-up, justification for the type of multivariate model used, a description of the factors placed in the model, and of those factors retained in the final model with their significance values. Such a detailed review is beyond the scope of this chapter.

The capability to measure a prognostic factor reliably and accurately is a prerequisite for its clinical use. The clinical applicability of a prognostic factor is based on a cost–effectiveness analysis, i.e., determining the relationship between the improvement in prognostic accuracy provided by the factor and the cost of determining the factor. In addition, if a prognostic factor is to be useful its analysis must be timely, and it cannot be so complex that it is restricted to research laboratories.

For over 40 years the International Union Against Cancer [28]/American Joint Committee on Cancer [4] have developed the TNM staging system. This system combines the variables tumor size and local extension (T), regional lymph node involvement (N), and metastatic spread (M). The TNM staging system has been very useful, but although it is the best system available, it is not extremely accurate.

Table 3. Molecular–genetic prognostic factors

Gene name[a]	Chromosome	Gene product	Literature support	Function	Expression	Properties	Detection method	References
nm23-H1 (current name NME-1)	17q1.1–2.1	nm23 protein[b]	+	Metastasis suppressor	Increased expression associated with good prognosis	Related to histologic grade and stage	Immuno-histochemical	26,50
p53 (current name TP53) Proto-oncogene	17q13.1	p53 protein[b]; nuclear phospho-protein	+	Suppressor gene; expressed in all cells late in late G1 phase	Accumulation of p53 protein associated with metastasis and reduced survival	Inversely associated with number of hormone receptors	Immuno-histochemical; detect p53 antibodies	15, 55
c-*myc*[b] (current name CMYC) Proto-oncogene	8q24	DNA-binding protein	+	Implicated in control of cell growth, differentiation and apoptosis	Amplification associated with poor prognosis; amplification occurs in 6%–10% of patients studied	Regulated by estrogen in hormone-dependent cells, also associated with hormone-independent cells	Quantitative polymerase chain reaction-based assay	44, 65
	6p21.3	Heat shock protein[b], hsp70, aka hspa1, 70 kDa	+	Involved in protein–protein interactions	High levels associated with shorter disease-free survival in node-negative patients, not overall survival	Associated with c-*myc* and p53; hormone related	Western blot, immuno-histochemical	10
	3, 9, X Three related human genes, not fully sequenced yet	Heat shock protein[b] hsp27, 27 kDa, aka p29, stress response protein srp-27	0		Does not have independent prognostic significance at 8-year follow-up	Hormone related	Northern and western blot, immuno-histochemical	11, 12, 61

RAS (Ha-, Ki-, N-) Proto-oncogene	Ha- 11p15 Ki – 12p12.1 N- 1p13	p21 RAS protein, 21 kDa	0	Related to cell division	Expressed in non-neoplastic breast; highest levels found in carcinomas	Intra-cytoplasmic vs. plasma membrane localization; equivocal relationship with ER	Semi-quantitative immuno-histochemical; different methods produce different results	23, 58
	11p15 (near Ha-RAS)	Cathepsin D[b] (three active forms), 34 kDa	0	Lysosomal protease	Increased expression associated with poor prognosis	Estrogen-regulated, can be induced by growth factors	Cytosolic preparations support; western blot, immuno-histochemical methods do not support	32, 46
	17q21-22	DNA Topo-isomerase II enzyme[b]	0	Marker of cellular proliferation; required for DNA replication, present in S-phase	Low levels suggest chemotherapeutic drug resistance	Prediction not well supported yet; inversely associated with ER, PR	Immuno-histochemical	53, 63
PS2	21q	PS2 protein[b], 84 amino acids aka pNR2, BCE1	+	Growth factor	Expression is associated with longer DFS and OS; may be a better predictor than estrogen	Gene expression controlled by estrogen; structurally similar to IGF	Northern blot; Immuno-histochemical	17, 48

Table 3 (*Contd.*)

Gene name[a]	Chromosome	Gene product	Literature support	Function	Expression	Properties	Detection method	References
	6q24-27	ER[b]	+	Growth factor	Predicts response to hormonal therapy; expression associated with improved DFS and OS	Hormone related	Immuno-histochemical	16, 25, 37
	11q23	PR[b]	+	Growth factor	In association with ER, improved DFS and OS in premenopausal women	Hormone related	Immuno-histochemical	5, 16, 62
C-*erb*B-2 (HER-2/neu) Proto-oncogene	17q21	p185[erbB2] 185-kDa transmembrane protein, 50% homology to EGF-R	+	Tyrosine kinase activity; possibly a growth factor receptor	Amplification or overexpression associated with decreased survival	Expressed in a minority of patients; most studies retrospective	Immuno-histochemical	43, 57
	7p13-p12	EGF-R[b]	+	Hormonally regulated positive growth factor (autoregulatory autocrine secretion)	Presence is associated with early recurrence and death	EGF secreted by macrophages; EGF-R is negatively correlated with ER and PR status	Immuno-histochemical	24, 42, 51
	IGF1–12q23 IGF2– 11p15.5	IGF I, II, aka Somatomedin C[b]	0	Stimulates cell proliferation in vitro (mitogenic)	Increased expression associated with poor prognosis	Associated with estrogen and progesterone	Western blot; radio-immunoassay	38, 45

	Aromatase[b]	0	Mediates conversion of precursors to estrone and estradiol	Not associated with DFS or OS	Hormone related	Quantification of tritiated water released from 1b-tritiated-androstene-dione	34
	Tissue polypeptide antigen[b]	+	Measures tumor activity	Expression associated with longer DFS and OS; also used to detect treatment response	Not hormone regulated	Immuno-histochemical	22,35
5q33	CSF-1	+	Stimulates the survival, proliferation, and differentiation of mononuclear phagocytes	Presence association with poor survival	CSF-1R expressed in monocytes and tumor cells	Immuno-histochemical	54

DFS, disease-free survival; OS, overall survival; ER, estrogen receptor; PR, progesterone receptor; IGF, insulin-like growth factor; CSF, colony-stimulating factor; EGF, epidermal growth factor; EGF-R, epidermal growth factor receptor; aka, also known as; +, well supported; 0, equivocal support.

[a] The gene name in the literature on prognostic factors is not always the current name for the gene.

[b] The aspect that is prognostic in the literature.

The integration of additional factors in the TNM stage model cannot easily occur for several reasons [8]. The TNM stage model is a look-up table based on a "bin" model. In a bin model, continuous variables are divided into discrete ranges (e.g., tumor size of 0–2 cm, 2.1–5 cm, more than 5 cm) and binary variables remain binary. One range of each variable (class) is placed in a bin, resulting in a mutually exclusive and exhaustive partitioning of the data space. Thus, in breast cancer, the TNM staging system is composed of 40 bins (five tumor classes × regional four lymph node classes × two metastasis classes). The bins are then grouped into stages by decreasing survival. In a bin model the number of bins increases exponentially with the number of variables. For example, if we added the variable histologic grade, with its four types, to the TNM staging system, the result is 160 bins (5 × 4 × 2 × 4). Thus, for any set of new variables, the number of bins that would have to be organized into stages would be enormous, the number of stages would increase, and the look-up table would become too complex to be useful. Further, because the accuracy of a bin/stage model depends on the number of patients in each bin, as the number of variables increase the number of bins increase, and the number of patients must increase exponentially to retain enough patients per bin to maintain accuracy.

This is not meant to suggest that the TNM variables should be eliminated. They are of major prognostic importance and will probably remain part of any prognostic system. What this does suggest is that, other than for anatomic extent, new prognostic factors should not be added to the TNM staging system to increase its predictive accuracy. However, prognostic factors may be integrated with the TNM variables in a new prognostic system for greater accuracy in predicting outcome.

As noted in the introduction, at least 76 putative prognostic factors for human breast cancer patients have been reported, and 37 are noted in Tables 1, 2, and 3. The American Joint Committee on Cancer has adopted criteria for the definition of a prognostic factor [8]. A prognostic factor is (1) statistically significant, i.e., its prognostic value only rarely occurs by chance, (2) independent, i.e., retains its prognostic value when combined with other factors, and (3) clinically relevant, i.e., has a major impact on prognostic accuracy.

With these criteria in mind, the College of American Pathologists (CAP) convened a multidisciplinary conference of invited participants, entitled the "*CAP Conference XXVI: Clinical Relevance of Prognostic Markers in Solid Tumors*", in Snowbird, Utah in June 1994. Prognostic markers for cancer of the breast, colorectum, and prostate were considered. The proceedings of this conference are being prepared for publication.

A large number of prognostic factors for breast cancer were reviewed, although epidemiologic factors were not considered. The participants identified two subsets of relevant prognostic factors that have been used clinically, as deemed appropriate by the managing physician.

Group I includes those prognostic factors that are well supported biologically and clinically in the scientific literature. These include the TNM variables. Also included are histologic type, grade (histologic/nuclear), and steroid recep-

tors (estrogen, progesterone). Group II includes prognostic factors extensively studied both biologically and clinically, and this group is divided into two subsets. The first of these, group IIA, includes prognostic factors that have been used in clinical trials, e.g., proliferation markers such as S-Phase fraction and Ki-67 (M1B1), and mitotic index (thymidine labeling index has been validated, but the complexity of the procedure does not lend itself to general clinical use at this time). The second subset, group IIB, includes prognostic factors in which biologic and clinical correlative studies have been carried out, but where there are few outcome studies, e.g., p53, c-erbB-2 (HER-2/neu), vascular invasion (lymphatic or venous), and angiogenesis. Group III includes others that do not currently meet the criteria for group I or group II. A large number of factors were discussed at the conference, including many of those in Tables 2 and 3 that are not in groups I or II. The conference participants concluded that these would not be listed since such a listing would be no more than a status report for June 24, 1994. With additional research, some may eventually meet the criteria for groups I or II, and others will doubtless be added to group III.

The CAP Snowbird Conference has effectively given perspective to the galaxy of putative prognostic factors for physicians responsible for the management of breast cancer patients. However, we must be cognizant that other prognostic factors that satisfy the criteria described may be assimilated into clinical practice when their value is proven.

References

1. Ansell D, Whitman S, Lipton R, Cooper R (1993) Race, income, and survival from breast cancer at two public hospitals. Cancer 72: 2974–2978
2. Barraclough J, Pinder P, Cruddas M, Osmond C, Taylor I, Perry M (1992) Life events and breast cancer prognosis. BMJ 304: 1078–1081
3. Bastarrachea J, Hortobagyi GN, Smith TL, Kau SC, Buzdar AU (1993) Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. Ann Intern Med 119: 18–25
4. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ (eds) (1992) Manual for staging of cancer, 4th edn. Lippincott, Philadelphia
5. Berger U, McClelland RA, Wilson P, Greene GL, Haussler MR, Oike JW et al (1991) Immunocytochemical determination of estrogen receptor, progesterone receptor, and 1,25-dihydroxyvitamin D3 receptor in breast cancer and the relationship to prognosis. Cancer Res 51: 239–244
6. Bianchi S, Paglierani M, Zampi G, Cardona G, Cataliotti L, Bonardi R et al (1993) Prognostic value of proliferating cell nuclear antigen in lymph node-negative breast cancer patients. Cancer 72: 120–125
7. Bloom H, Richardson W (1957) Histological grading and prognosis in breast cancer. Br J Cancer 9: 359–377
8. Burke HB, Henson DE (1993) Criteria for prognostic factors and for an enhanced prognostic system. Cancer 72: 3131–3135
9. Carter CL, Allen C, Henson DE (1988) Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 63: 181–187
10. Ciocca DR, Clark GM, Tandon AK, Fuqua SAW, Welch WJ, McGuire WL (1993) Heat shock protein hsp70 in patients with axillary lymph node-negative breast cancer: prognostic implications. J Natl Cancer Inst 85: 570–574

11. Ciocca DR, Luque EH (1991) Immunological evidence for the identity between the hsp27 estrogen-regulated heat shock protein and the p29 estrogen receptor-associated protein in breast and endometrial cancer. Breast Cancer Res 20: 33–42
12. Ciocca DR, Oesterreich S, Chamness GC, McGuire WL, Fuqua SAW (1993) Biological and clinical implications of heat shock protein 27 000 (Hsp27): a review. J Natl Cancer Inst 85: 1558–1570
13. Clayton F, Hopkins CL (1993) Pathologic correlates of prognosis in lymph node-positive breast carcinomas. Cancer 67: 11780–11790
14. Coates A, Gebski V, Signorini D, Murray P, McNeil D, Byrne M et al (1992) Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. J Clin Oncol 10: 1833–1838
15. Davidoff AM, Herndon JE, Glover NS, Kerns BM, Pence JC, Inglehart JD, Marks JR (1991) Relation between p53 overexpression and established prognostic factors in breast cancer. Surgery 110: 259–264
16. Fisher B, Redmond C, Fisher ER, Caplan R (1988) Relative worth of estrogen and progesterone receptors and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients. J Clin Oncol 6: 1076–1087
17. Foekens JA, van Putten WJ, Portengen H, de Koning H, Thirion B, Alexieva-Figusch J, Klijn JM (1993) Prediction of relapse and survival in breast cancer patients by pS2 protein status. J Clin Oncol 11: 899–908
18. Garne JP, Aspegren K, Linell F, Rank F, Ranstam J (1994) Primary prognostic factors in invasive breast carcinoma with special reference to ductal carcinoma and histologic malignancy grade. Cancer 73: 1438–1448
19. Gaspirini G, Weidner N, Bevilacqua P, Maluta S, Palma PD, Caffo O et al (1994) Tumor microvessel density, p53 expression, tumor size, and peritumoral lymphatic invasion are relevant prognostic markers in node-negative breast carcinoma. J Clin Oncl 12: 454–466
20. Gilchrist KW, Gray R, Fowble B, Tormey DC, Taylor SG (1993) Tumor necrosis is a prognostic predictor for early recurrence and death in lymph node-positive breast cancer: a 10-year follow-up study of 728 eastern cooperative oncology group patients. J Clin Oncol 11: 1929–1935
21. Gilchrist KW, Kalish L, Gould VE, Hirschl S, Imbriglia JE, Levy WM et al (1985) Interobserver reproducibility of histopathology features in stage II breast cancer: an ECOG study. Breast Cancer Res Treat 5: 3–10
22. Gion M, Mione R, Pappagallo GL, Gatti C, Nascimben O, Brandes A et al (1992) Tissue polypeptide antigen in breast cancer cytosol: a new effective prognostic factor. Eur J Cancer 29A: 66–69
23. Going JJ, Anderson TJ, Wyllie AH (1992) Ras p21 in breast tissue: association with pathology and cellular localization. Br J Cancer 65: 45–50
24. Gullick WJ (1991) Prevalence of aberrant expression of the epidermal growth factor receptor in human cancers. Br Med Bull 47: 87–98
25. Hahnel R (1983) Oestrogen receptors and breast carcinoma. Med J Aust 1: 350–351
26. Hennessy C, Henry JA, May FEB, Westley BR, Angus B, Lennard TW (1991) Expression of the antimetastatic gene nm23 in human breast cancer: association with good prognosis. J Natl Cancer Inst 83: 281–285
27. Henson DE, Ries L, Freedman LS, Carriaga M (1991) Relationship among outcome, stage of disease, and histologic grade for 22,616 cases of breast cancer. Cancer 68: 2142–2149
28 Hermanek P, Sobin LH (eds) (1992) UICC TNM classification of malignant tumours, 4th edn, 2nd revision. Springer, Berlin Heidelberg New York Tokyo
29. Ip C (1993) Controversial issues of dietary fat and experimental mammary carcinogenesis. Prev Med 22: 728–737
30. Joensuu H, Toikkanen S (1992) Identification of subgroups with favorable prognosis in breast cancer. Acta Oncol 31: 293–301
31. Kamby C (1990) The pattern of metastases in human breast cancer: methodologic aspects and influence of prognostic factors. Cancer Res Treat 17: 37–61
32. Kandalaft PL, Chang KL, Ahn CW, Traweek ST, Mehta P, Battifora H (1993) Prognostic significance of immunohistochemical analysis of Cathepsin D in low-stage breast cancer. Cancer 71: 2756–2763
33. Komitowski D, Janson C (1990) Quantitative features of chromatin structure in the prognosis of breast cancer. Cancer 65: 2725–2730
34. Lipton A, Santen RJ, Santner SJ, Harvey HA, Sanders SI, Matthews MA (1992) Prognostic value of breast cancer aromatase. Cancer 70: 1951–1955

35. Mansour O, Motawi T, Khaled H, el-Ahmady O (1993) Clinical value of thymidine kinase and tissue polypeptide specific antigen in breast cancer. Dis Markers 11: 171–177

36. McGuire WL, Clark GM (1992) Prognostic factors and treatment decisions in axillary-node-negative breast cancer. N Engl J Med 326: 1756–1761

37. McGuire WL, Clark GM, Dressler LG, Owens MA (1986) Role of steroid hormone receptors as prognostic factors in primary breast cancer. NCI Monogr 1: 19–23

38. McGuire WL, Jackson JG, Figueroa JA, Shimasaki S, Powell DR, Yee D (1992) Regulation of insulin-like growth factor-binding protein (IGFBP) expression by breast cancer cells: use of IGFBP-1 as an inhibitor of insulin-like growth factor action. J Natl Cancer Inst 84: 1336–1341

39. Meyer JS, Koehm SL, Hughes JM, Higa E, Wittliff JL, Lagos JA, Manes JL (1993) Bromo-deoxyuridine labeling for S-phase measurement in breast carcinoma. Cancer 71: 3531–3540

40. Nguyen M, Watanabe H, Budson AE, Richie JP, Hayes DF, Folkman J (1994) Elevated levels of an angiogenic peptide, basic fibroblast growth factor, in urine of patients with a wide spectrum of cancers. J Natl Cancer Inst 86: 356–361

41. O'Neill KL, Hoper M, Odling-Smee GW (1992) Can thymidine kinase levels in breast tumors predict disease recurrence? J Natl Cancer Inst 84: 1825–1828

42. O'Sullivan C, Lewis CE, Harris AL, McGee JO (1993) Secretion of epidermal growth factor by macrophages associated with breast carcinoma. Lancet 342:148–149

43. Perren TJ (1991) c-erbB-2 oncogene as a prognostic marker in breast cancer. Br J Cancer 63: 328–332

44. Pertschuk LP, Feldman JG, Kim DS, Nayeri K, Eisenberg KB, Carter AC et al (1993) Steroid hormone receptor immunochemistry and amplification of c-myc protooncogene. Cancer 71: 162–171

45. Pollak M, Costantino J, Polychronakos C, Blauer S, Guyda H, Redmond C et al (1990) Effects of tamoxifen on serum insulin-like growth factor I levels in stage I breast cancer patients. J Natl Cancer Inst 82: 1693–1697

46. Ravdin PM, Tandon AK, Allred DC, Clark GM, Fuqua AW, Hilsenbeck SH et al (1994) Cathepsin D by western blotting and immunohistochemistry: failure to confirm correlations with prognosis in node-negative breast cancer. J Clin Oncol 12: 467–474

47. Ries LA, Henson DE, Harras A (1994) Survival from breast cancer according to tumor size and nodal status. Semin Surg Oncol 3: 35–53

48. Rio MC, Chambon P (1990) The pS2 gene, mRNA and protein: a potential marker for human breast cancer. Cancer Cells 2:269–274

49. Rochefordiere AD, Asselain B, Campana F, Scholl SM, Fenton J, Vilcoq JR et al (1993) Age as prognostic factor in premenopausal breast carcinoma. Lancet 341: 1039–1043

50. Royds JA, Stephenson TJ, Rees RC, Shorthouse AJ, Silcocks PB (1993) Nm23 protein expression in ductal in situ and invasive human breast carcinoma. J Natl Cancer Inst 85: 727–731

51. Sainsbury JR, Farndon JR, Needham GK, Malcolm AJ, Harris AL (1987) Epidermal-growth-factor receptor status as predictor of early recurrence of and death from breast cancer. Lancet 1 (8547): 1398–1402

52. Satariano WA, Ragland DR (1994) The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 120: 104–110

53. Schneider E, Horton JK, Yang CH, Nakagawa M, Cowen KH (1994) Multidrug resistance-associated protein gene overexpression and reduced drug sensitivity to topoisomerase II in a human breast carcinoma MCF7 cell line selected for etoposide resistance. Cancer Res 54: 152–158

54. Scholl SM, Pallud C, Beuvon F, Hacene K, Stanley ER, Rohtschneider L et al (1994) Anti-colony-stimulating-factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. J Natl Cancer Inst 86: 120–126

55. Silvestrini R, Benini E, Daidone MG, Veneroni S, Boracchi P, Cappelletti V et al (1993) p53 as an independent prognostic marker in lymph node-negative breast cancer patients. J Natl Cancer Inst 85: 965–970

56. Silvestrini R, Daidone MG, Gasparini G (1985) Cell kinetics as a prognostic marker in node-negative breast cancer. Cancer 56:1982–1987

57. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235: 177–182

58. Spandidos DA, Agnantis NJ (1984) Human malignant tumours of the breast, as compared to their respective normal tissue, have elevated expression of the Hervey ras oncogene. Anticancer Res 4: 269–272

59. Steele GD, Winchester DP, Menck HR, Murphy GP (eds) (1993) National Cancer Data Base annual review of patient care, 1993. American Cancer Society, Atlanta
60. Stenman U, Heikkinen R (1991) Serum markers for breast cancer. Scand J Clin Lab Invest 206: 52–59
61. Thor A, Benz C, Moore D, Goldman E, Edgerton S, Landry J et al (1991) Stress response protein (srp-27) determination in primary human breast carcinomas: clinical, histologic, and prognostic correlations. J Natl Cancer Inst 83: 170–178
62. Thorpe SM, Rose C (1986) Oestrogen and progesterone receptor determinations in breast cancer: technology and biology. Cancer Serv 5: 505–525
63. Tuccari G, Rizzo A, Giuffre G, Barresi G (1993) Immunohistochemical detection of DNA topoisomerase type II in primary breast carcinomas: correlation with clinico-pathological features. Virchows Arch [A] 423: 51–55
64. Veronese SM, Gambacorta M, Gottardi O, Scanzi F, Ferrari M, Lampertico P et al (1993) Proliferation index as a prognostic marker in breast cancer. Cancer 71: 3926–3931
65. Watson PH, Safneck JR, Le K, Dubik D, Shiu RPC (1993) Relationship of c-myc amplification to progression of breast cancer from in situ to invasive tumor and lymph node metastasis. J Natl Cancer Inst 85: 902–907
66. Weidner N, Folkman J, Pozza F, Bevilacqua P, Allred EN, Moore DH et al (1992) Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast cancer. J Natl Cancer Inst 84: 1875–1887
67. Weikel W, Beck T, Mitze M, Knapstein PG (1991) Immunohistochemical evaluation of growth fractions in human breast cancers using monoclonal antibody Ki-67. Breast Cancer Res Treat 18: 149–154
68. Werner M, Faser C, Silverberg M (1993) Clinical utility and validation of emerging biochemical markers for mammary adenocarcinoma. Clin Chem 39: 2386–2396
69. Yahan SR, Neuberg DS, Dieffenbach A, Yacoub L (1993) Prediction of early relapse and shortened survival in patients with breast cancer by proliferating cell nuclear antigen score. Cancer 71: 3552–3559
70. Yates JW, Chalmer B, McKegney FP (1980) Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 45: 2220–2224