REVIEW ARTICLE

Unopposed oestrogen and survival of breast cancer

R. A. Badwe, M. S. Bhansali and J. S. Vaidya*

*Department Of Surgical Oncology, Tata Memorial Centre, Bombay, India, *Department of Surgery, University College London, London, UK*

S U M M A R Y. It has been suggested that survival of breast cancer patients may be affected by their hormonal milieu. the level of circulating oestrogen in a woman's body changes with the phase of menstrual cycle, the amount of body fat and her menopausal status. We examined whether these factors affect survival from breast cancer. Meta-analysis of relevant literature for age (reflecting menopausal status; 22 studies), timing of surgery during the menstrual cycle in premenopausal women (28 studies) and body weight in postmenopausal women (18 studies), was carried out to determine the effect of unopposed oestrogen at the time of surgery on survival in breast cancer. The meta-analyses revealed a significantly better survival in premenopausal vs postmenopausal patients (OR 0.76, CI 0.74–0.78, $2P < 0.0000001$), in patients who were operated in the luteal vs follicular phase of the menstrual cycle (OR 0.87, CI 0.79–0.97, $2P < 0.02$), and in postmenopausal women who were not obese vs obese (OR 0.64, CI 0.59–0.70 $2P < 0.0000001$). These data indicate that unopposed oestrogen at the time of surgery may have a deleterious effect on survival in women of all ages. It prompts future research into changing the hormonal milieu at the time of surgery as a means of improving survival.

INTRODUCTION

The importance of hormonal milieu in patients with breast cancer has been stressed in the past by Beatson[1] and Mueller et al.[2] This was resurrected by Ratajczak et al[3] and Hrushesky et al[4] by suggesting that timing of surgical intervention during the menstrual cycle can influence the long-term outcome. They suggested that surgery during the periovulatory phase (days 7–20 after last menstrual period) was safe compared with surgery performed during the perimenstrual phase (days 0–6 and 21–32 after the last menstrual period). Unfortunately, many others could not reproduce this effect.[5–7] The debate was rekindled with a new hypothesis by Badwe et al[8] and reached a crescendo with the recent publication by Veronesi et al from Milan.[9] The hypothesis suggested a poor outcome when surgery was performed during the phase of unopposed oestrogen, i.e. the follicular phase. The new hypothesis was derived from the findings that treatment of breast cancer in perimenopausal women had a poor outcome.[10] These findings were supported by at least two other studies.[11,12] It was thought that poor outcome could be attributed to the endogenous hormonal milieu. It is likely that these women experience

anovulatory cycles more frequently and hence are exposed to unopposed oestrogen more often than premenopausal women and of greater magnitude of unopposed oestrogen compared with postmenopausal women.

If the hypothesis were true then the deleterious effect of unopposed oestrogen should be evident in all states of menopause. The possibility that a patient may experience unopposed oestrogenic milieu is based on the established endocrine changes during the lifetime of a woman.[13] We have attempted to test the hypothesis in the situations mentioned below, performing a meta-analysis of unpublished and published reports in English language using standard methods.[14]

1. Peri- and postmenopausal women are more likely to have unopposed oestrogen compared with premenopausal women, as in the latter group, at least 50% of the time, oestrogens are opposed by progesterones (luteal phase).
2. Premenopausal women are exposed to unopposed oestrogen during the follicular phase (days 0–14) whereas in the luteal phase (days 15–32), progesterones oppose oestrogens.
3. In postmenopausal women, the source of oestrogen is the enzyme aromatase in body fat,[15] which converts precursors of oestrogen into the active hormone. Obese women produce more oestrogen than thin women.[16]

Address correspondence to: R. A. Badwe MS, Assistant Surgeon, Department of Surgical Oncology, Tata Memorial Hospital, Parel, Bombay 400 012, India

METHODS

Meta-analysis of relevant literature

Meta-analyses were performed to address each of the following issues with reference to breast cancer.

1. Age, reflecting menopausal status, i.e. premenopausal ($\leq$ 50 years) vs peri-postmenopausal ($\geq$50 years).
2. Timing of surgery during the menstrual cycle in premenopausal women. Those operated on during the unopposed (follicular) vs opposed (luteal) oestrogenic milieu in menstrual cycle. Unopposed oestrogenic milieu was either defined as the follicular phase or days 2–11 after the last menstrual period, or, in one study, based on actual measurements of hormonal status.[17] In the second group, few patients within the follicular phase may have been included in the luteal phase, leading to an underestimation of the expected deleterious effect of unopposed oestrogen.
3. Obesity in postmenopausal women: obese vs non-obese. Obesity in reality is a continuous variable as is evident in one of the largest studies.[18] Dichotomy by any cut-off as perceived by individual authors would be the best expression of the effect.

Meta-analyses were conducted in accordance with the reporting standard described by Halvorsen et al.[19]

Literature search

The literature search for meta-analyses was carried out through *Index Medicus* (1975–1983) and computer archives (*Oncodisc* 1984–1994) based on medical subject heading key words (eg. breast cancer, surgery, menstrual cycle, obesity, body weight, age, etc.), by searching bibliographies of relevant texts, by searching cross-references from studies and review articles as they were obtained, by meeting abstracts and by conference presentations. Articles are not reported in any particular order.

Eligibility criteria

Criteria for inclusion of a study in the meta-analysis were established for each of the three issues under investigation.

For comparing the impact of hormones on either side of menopause, studies stratifying patients as pre-, peri- and postmenopausal were included. Premenopausal women were those experiencing regular/irregular periods; the rest were considered as postmenopausal. Studies addressing age as prognostic indicator were included only when regrouping was possible on either side of the age of 50 years with the assumption that the majority of women below the age of 50 are premenopausal; to reduce the impact of other prognos-

tic factors, only studies with a large number of patients (>500) were considered.

For timing of surgery, the study should have included premenopausal patients with operable breast cancer and the menstrual cycle intervals should have been unambiguously stratified as opposed and unopposed oestrogen milieu. For obesity, the only eligibility criterion was that the patients should be postmenopausal. All the searched articles with age as a prognostic factor met the above criteria and were included in the meta-analysis. For the timing of surgery, four studies[20–23] were excluded, as in three studies the precise number of survivors and deaths in each arm were not available and one of them was not grouped into follicular and luteal phases. It is important to note that three of the four studies supported the hypothesis of deleterious impact of unopposed oestrogen at the time of surgery.

For obesity, one of the searched studies was rejected because data were stratified into multiple subgroups.[18] Two articles[24–25] that were included had minor deviation from the eligibility criteria: both included premenopausal women, but the number was small.

Number of studies included

A total of 22 articles[2,10–12,26–43] were included for meta-analysis on age as a prognostic factor, 28 studies in 27 articles[4,8,9,17,44–66] for timing of surgery, and 18 articles[24,25,67–82] for obesity as a prognostic factor.

Study design

All studies were retrospective observational studies. For discrete objective variables like age and obesity, retrospective data are unlikely to differ significantly from prospective data. For timing of surgery, prospective data would be more accurate and desirable. However, in the absence of any published prospective trial to date, retrospective studies were considered. It is less likely that there would be a publication bias on this topic because of its controversial nature, and we believe that studies reporting either a positive or a negative correlation would be equally likely to be published.

Results used in combining the overall survival at the end of 5 years reported in the studies were used to determine the mortality for each study. Where the exact 5 year survival figures were not reported they were deduced by careful measurement from the survival curves. In the instances where survival data were not given, the 5-year disease-free data were used instead. Almost all studies had a minimum follow-up period of 5 years or more.

Statistical methods

The difference between the observed and expected (O–E)

incidence in mortality as well as variance was calculated for each study using standard methodology.[83] The odds ratio (OR) defined as ratio of mortality rate in the treatment group to control group was obtained for each trial. The individual variances and the event rates were combined to obtain pooled odds ratio (POR) with confidence intervals (CI) and per cent reduction in the POR using the Mantel Haenszel technique. A fixed-effect model was used for calculating the effect size. The formal χ^2 test for heterogeneity was applied to all three meta-analyses to test for the homogeneity of the different studies included in each.

RESULTS

Age as a prognostic factor, reflecting the menopausal status

Twenty-two studies were included in the meta-analysis. In 15 studies, premenopausal women had better survival, and the results were equivocal in 7 studies. The meta-analysis revealed a significantly higher survival in premenopausal women (OR 0.76, CI 0.74–0.78, $2P < 0.0000001$) with an odds reduction of 24% ± 1 (Fig. 1).

Timing of surgery in premenopausal women

Twenty-eight studies were included in the meta-analysis. In 6 studies, those women who were operated on in the luteal phase of the menstrual cycle had better survival, whereas in 3 studies, those who were operated in the follicular phase

had better survival. The results were equivocal in 19 studies. The meta-analysis revealed better survival in those women who were operated on in the luteal phase of the menstrual cycle (OR 0.87, CI 0.79–0.97, $2P < 0.02$) with an odds reduction of 12.8% ± 5 (Fig. 2).

Although the test for heterogeneity was positive, it did not invalidate the standard overview techniques used to analyse the trials. Since studies vary in terms of number of patients, the effect size might show wide variation, and although a positive test for heterogeneity may challenge the magnitude of effect, it did not rule out the presence of the effect.

Obesity in postmenopausal women as a prognostic factor

Eighteen studies were included in the meta-analysis. In 12 studies, non-obese women had better survival than obese women, whereas in 6 studies, the results were equivocal. None of the studies reported a higher survival rate for obese women. The meta-analysis revealed a significantly higher survival rate in non-obese women (OR 0.64, CI 0.59–0.70, $2P < 0.0000001$) with an odds reduction of 36.6 ± 3.7 (Fig. 3).

DISCUSSION

Meta-analyses of published data suggest that the presence of unopposed oestrogen at the time of surgery may be deleterious to breast cancer patients. The meta-analysis depicted
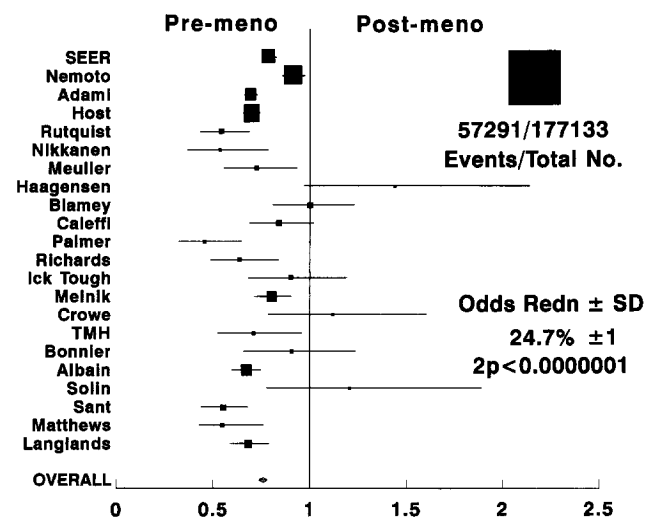

Fig. 1 Meta-analysis of studies with menopausal status as prognostic factor in breast cancer. Test of heterogeneity $P < 0.001$. Large square to the right, top corner depicts the information content of the whole meta-analysis. The small square for each study indicates its information content and the lines on either side represent 95% confidence intervals. The diamond at the bottom of each figure represents the overall effect and its confidence limits (95%).
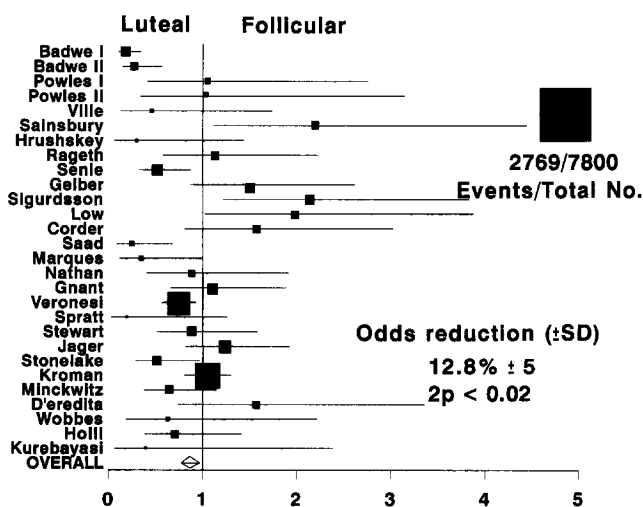

Fig. 2 Meta-analysis of studies with timing of surgery during the menstrual cycle in breast cancer. Test of heterogeneity $P < 0.001$. For key to symbols, see legend to Figure 1.
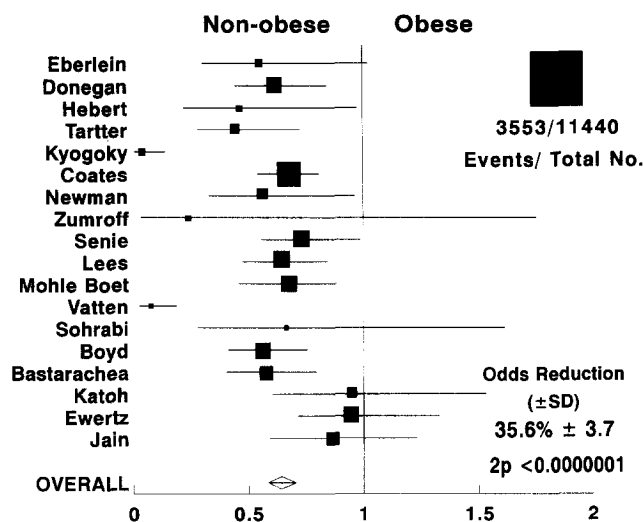
Fig. 3 Meta-analysis of studies with obesity as prognostic factor in breast cancer. Test of heterogeneity $P < 0.001$. For key to symbols, see legend to Figure 1.

poor survival in peri-postmenopausal women compared with premenopausal women, which is contrary to the conventional belief that breast cancer after the menopause is less fatal. Poor survival in perimenopausal women is also seen unequivocally in our hospital data[10] and at least two other studies corroborate our finding.[11,12]

The meta-analysis of the studies on timing of surgery showed that the distribution of results is not normal. Such lack of homogeneity could be due to one or more of the following three reasons. First the questionable reliability of retrospective data. Second, differences in patient management protocol, e.g. timing of needle biopsy, mammography and definitive surgery. The second study from Guy's hospital[44] suggested that these procedures may affect the outcome of surgery independently. Finally, most of the effect of timing of surgery was evident in patients with lymph node metastases,[8,9,45] hence this effect may not be evident if the majority of patients in the study did not have lymph node metastases. It is curious that the three large studies[8,9,47] have shown that the risk of death is directly proportional to the concentration of circulating oestrogens in the follicular phase. Such a quantitative relationship between circulating oestrogen and risk of death is also evident in the meta-analysis on body fat and survival in postmenopausal women with breast cancer. Is it possible to support such a strong body of clinical data with logical mechanisms based on biology?

Oestrogens are known to modulate at least two proteases in vitro (Cathepsin D and plasminogen activator urokinase).[84,85] These two proteases bestow invasive potential on the primary tumour.[86] The ability of the primary tumour to secrete these proteases has been inversely correlated with survival from breast cancer.[84,85] It is also possible that the

process of digestion can reduce the pericellular pH using ionic calcium, which is the only extracellular buffer. This non-availability of calcium can reduce the function of epithelial cadherins, the molecules which maintain the adhesive property of cells.[87] This in turn allows cells to be less adhesive and free to metastasize. Such lack of adhesion and increased exfoliation is evident under the oestrogen influence in endometrial cells during the menstrual cycle.[88] These two mechanisms of invasion and lack of adhesion can increase the metastatic potential of tumour cells. The disseminated tumour cells, when nestled at distant sites, may be well supported for survival due to increased expression of bcl-2 oncogene preventing apoptosis[89] and proliferation by growth factors under the oestrogen stimulus.[90] The establishment of micrometastases is prevented by the natural host defence mechanism of natural killer (NK) cells.[91] The NK cell activity is suppressed by circulating oestrogens, producing a permissive environment for development of micrometastases.[92] Progesterones oppose oestrogen action at the peripheral target tissues and this effect is probably due to its ability to upregulate activity of 17 beta-hydroxy-steroid dehydrogenase, an enzyme which metabolizes oestrogens into inactive compounds.[93]

A spin-off from these data is that events at the time of surgery may influence the growth of metastases and long-term survival. This has been suggested previously by Tyzzer[94] and Nissen-Myer.[95] Malignant cells in the circulation at the time of surgery were first demonstrated by Fisher & Turnbull.[96] Interest in this field has been rekindled by the availability of polymerase chain reaction technology, which has improved the sensitivity of detection of cells in circulation. Recent studies have shown an increase in epithelial cells in the circulation at the time of surgery.[97,98] Whatever the mechanisms, if these findings are substantiated in prospective studies, the hypothesis offers a sizable survival advantage by implementing a simple manoeuvre. It also offers insight into the process and timing of the establishment/autonomy of micrometastases which will justify using modifiers of metastatic potential (tamoxifen, progesterone, inhibitors of proteases) in the neoadjuvant setting.

References

1. Beatson C T. On treatment of inoperable cases of carcinoma of the mamma suggestions for new methods of treatment with illustrative cases. Lancet 1896; 2: 104–107.
2. Meuller C B, Ames F, Anderson G D. Breast cancer in 3558 women: age as a significant prognostic determinant in the rate of dying and causes of death. Surgery 1978; 83: 123–132.
3. Ratajczak H V, Sothern R B, Hrushesky W J M. Estrous influence on surgical cure of mouse breast cancer. J Exp Med 1988; 168: 73–83.
4. Hrushesky W J M et al. Menstrual influence on surgical cure for breast cancer. Lancet 1989; 2: 949–952.
5. Gelber R, Goldhirsch A. Menstrual effect on surgical cure of breast cancer. Lancet 1989; 2: 1344.

6. Powles T J, Jones S E, Ashley S, Tidy A. Menstrual effect on surgical cure of breast cancer. Lancet 1989; 2: 1343–1344.
7. Ville Y, Larsy S, Spyratos F et al. Menstrual status and breast cancer surgery. Breast Cancer Res Treat 1990; 16: 119.
8. Badwe R A, Gregory W M, Chaudary M A et al. Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. Lancet 1991; 337: 1261–1264.
9. Veronesi U, Luini a, Mariani L et al. Effect of menstrual phase on surgical treatment of breast cancer. Lancet 1994; 343: 1544–1546.
10. Badwe R A, Havaldar R. Timing of surgery in breast cancer (letter). Lancet 1994; 344: 404.
11. Caleffi M, Fentiman I S. Factors at presentation influencing the prognosis in breast cancer. Eur J Cancer Clin Oncol 1989; 25: 51–56.
12. Langlands A O, Pocock S J, Kerr G R, Gore S M. Longterm survival of patients with breast cancer; a study of the curability of the disease. BMJ 1979; 2: 1247–1251.
13. Yen S. Physiology of menstrual cycle. In: Yen S, Jaffe R B, eds. Reproductive endocrinology. Philadelphia: WB Saunders, 1986: 126–151.
14. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. Oxford: Oxford University Press, 1990.
15. Grodin J M, Siiteri P K, MacDonald P C. source of estrogen production in postmenopausal women. J Clin Endocrinol Metab 1973; 36: 207–214.
16. Trichopoulos D, Brown J, MacMahon B. Urine estrogens and breast cancer risk factors among post-menopausal women. Int J Surg 1987; 40: 721–725.
17. Ville Y, Briere M, Lasry S et al. Timing of surgery in breast cancer (letter). Lancet 1991; 337: 1604–1605.
18. Tretli S, Haldorson T, Ottestad L. The effect of premorbid height and weight on survival of breast cancer patients. Br J Cancar 1990; 62: 299–303.
19. Halvorsen K T, Burdick E, Colditz G A et al Reporting standards in meta-analysis. In: Mosteller F, Bailer J C, eds. Boston: Medical uses of statistics. N Engl J Med Books, 1992: 413–426.
20. Von Minckwitz G, Kaufman M et al Timing of surgery during the menstrual cycle in operable breast cancer (abstr). Lancet meeting on challenge of breast cancer, April 1994: 77.
21. Engele L, Yaunalksne I, Berzins J, Nikitina M. Timing of radical mastectomy, immune parameters and 5 year survival in premenopausal breast cancer patients (abst). Eur J Cancer 1994; 30A(S2): S70–S75.
22. Callies R, Klemt W, Regidor P, Hoyme W. Timing of surgery in the menstrual cycle and operable breast cancer. Arch Gynecol Obstet 1993; 254: 787–789.
23. Donegan W L, Shah D, Wood W C. Prognosis of patients with breast cancer related to timing of surgery. Arch Surg 1993; 128: 309–313.
24. Sohrabi A, Sandoz J, Spratt J S, Polk H C. Recurrence of breast cancer obesity, tumour size and axillary lymph node metastases. JAMA 1980; 244: 264–265.
25. Bastarachea J, Hortobagyi G N, Smith M S, Kans W C, Buzdar A U. Obesity as an adverse prognostic factors for patients receiving adjuvant chemotherapy for breast cancer. Ann Intern Med 1994; 120: 18–25.
26. Adami H O, Malker B, Holmberg L et al. The relation between survival and age at diagnosis in breast cancer. N Engl J Med 1986; 315: 559–563.
27. Host H, Lund E. Age as a prognostic factor in breast cancer. Cancer 1986; 57: 2217–2221.
28. Rutquist L E, Wallgren A. The influence of age on outcome in breast cancer. Acta Radiol Oncol 1983; 22: 289–294.
29. Kleinfeld G, Haagensen C D, Cooley E. Age and menstrual status as prognostic factors in carcinoma breast. Ann Surg 1963; 157: 600–605.
30. Blamey R W. Premenopausal breast cancer: update on management. Medical Dialogue 1992; 355: 1–2.
31. Tough I C K. The menopause and prognosis in breast cancer. J R Coll Surg Edinb 1969; 14: 337–339.
32. Melnik U, Slater P E, Katz L, Davies A M. Breast cancer in Israel 1960–75, effect of age and origin on survival. Eur J Cancer 1980; 16: 1017–1023.
33. Palmer M K, Lythgoe J P, Smith A. Prognostic factors in breast cancer. Br J Surg 1982; 69: 697–698.
34. Gloeckler R, Pollack E S, Young J L. Cancer patient survival: SEER program 1973–79. J Natl Cancer Inst 1983; 70: 693–707.
35. Nemoto T, Vana J, Bedwani R N et al. Management and survival of female breast cancer: results of national survey by American College of Surgeons. Cancer 1980; 45: 2917–2924.
36. Richards G E. Mammary cancer: the place of surgery and radiotherapy in its management. Br J Radiol 1948; 21: 109–127.
37. Nikkanen V, Linna M, Toikanen S. Treatment results in mammary cancer stage I–IV. Acta Radiol Oncol Radit Phys Biol 1981; 20: 9–18.
38. Crowe J P, Gordon N H, Shenk R R et al. Age does not predict breast cancer outcome. Arch Surg 1994; 129: 483–488.
39. Bonnier P, Romain S, Charpin C et al. Age as a prognostic factor in breast cancer: relationship to pathologic and biologic features. Int J Cancer 1995; 62: 138–144.
40. Albain K S, Allred D C, Clark G M. Breast cancer outcome and predictors of outcome: are there age differentials? Monogr Natl Cancer Inst 1994; 16: 35–42.
41. Solin J S, Fowble B, Schultz D J, Goodman R L. Age as a prognostic factor for patients treated with definitive irradiation for early breast cancer. Int J Radiat Oncol Biol Phys 1989; 16: 373–381.
42. Sant M, Gatta G, Micheli A et al. Survival and age at diagnosis of breast cancer in a population based cancer registry. Eur J Cancer 1991; 27: 981–984.
43. Matthews R H, McNeese M D, Montague E D, Oswald M J. Prognostic implication of age in breast cancer patients treated with tumorectomy and irradiation or with mastectomy. Int J Radiat Oncol Biol Phys 1988; 14: 659–663.
44. Badwe R A, Fentiman I S, Richards M A et al. Surgical procedures, menstrual cycle phase and prognosis in operable breast cancer. Lancet 1991; 338: 815–816.
45. Senie R T, Rosen P P, Rhodes P, Lesser M L Timing of breast cancer excision during the menstrual cycle influences duration of disease free survival. Ann Intern Med 1991; 115: 337–342.
46. Sainsbury R, Jones M, Parker D et al. Timing of surgery in breast cancer (letter). Lancet 1991; 338: 392.
47. Goldhirsch A, Gelber R, Forbes J et al. Timing of surgery in breast cancer (letter). Lancet 1991; 338: 691–692.
48. Low S C, Galea M H, Blamey R W. Timing of breast cancer surgery (letter). Lancet 1991; 338: 691.
49. Powles T J, Ashley S E, Nash A G et al. Timing of surgery in breast cancer (letter). Lancet 1991; 337: 1604.
50. Rageth J C et al. Timing of breast cancer surgery within the menstrual cycle: influence of lymph node involvement, receptor status, postoperative metastatic spread and local recurrence. Ann Oncol 1991; 2: 269–272.
51. Gnant M F X, Seifert M, Jakesz R et al. Breast cancer and timing of surgery during menstrual cycle. A 5-yr analysis of 385 premenopausal women. Int J Cancer 1992; 52: 707–712.
52. Stewart H. Does the menstrual timing of surgery in breast cancer affect survival? Results from other centres. Paper presented at the symposium on the treatment of breast cancer in premenopausal women, 14–15 August 1991, King's College, Cambridge.
53. Nathan B, Bates T, Anbazhagan R, Norman A R. Timing of surgery in relation to menstrual cycle and survival in premenopausal women with breast cancer. Br J Surg 1993; 80: 43.
54. Sigurdsson H et al. Timing of surgery in the menstrual cycle does not appear to be a significant determinant of outcome in primary breast cancer. Doctoral dissertation, Lund University, 1992: 1-10.
55. Saad Z, Bramwell V, Duff J et al. Timing of surgery in relation to menstrual phase and its impact on survival in early breast cancer. Br J Surg 1994; 81: 217–220.
56. Marques L A, Franco E L. Association between timing of surgery during the menstrual cycle and prognosis in premenopausal breast cancer. Int J Cancer 1993; 53: 707–708.

57. Spratt J S, Zirnheld J, Yancey J M. BCDDP data can determine whether prognosis of breast cancer is affected by timing of surgery during the menstrual cycle. J Surg Oncol 1993; 53: 4–9.

58. Corder A P, Cross M, Julions S A et al. Timing of surgery and breast cancer. Postgrad J Med 1994; 68: 137–139.

59. Jaeger J. Timing of surgery during the menstrual cycle does not influence survival in breast cancer. Ann Oncol 1994; 5: 24–28.

60. Wobbes T, Thomas C M, Segers M F et al. The phase of menstrual cycle has no influence on the disease free survival of patients with mammary cancer. Br J Cancer 1994; 69: 599–600.

61. Stonelake P S, Powell J, Warwick J et al. Timing of surgery during the menstrual cycle in operable breast cancer. Br J Cancer 1993; 67: SXX:16.

62. Kroman N, Hojgaard A, Andersen K W et al. Timing of surgery in relation to menstrual cycle does not predict the prognosis in primary breast cancer. Eur J Surg Oncol 1994; 20: 430–435.

63. Von-Minckwitz G, Kaufmann M, Dobberstein S, Grischke E M, Diel I J. Surgical procedure can explain varying influence of menstrual cycle on prognosis of premenpausal breast cancer patients. The Breast 1995; 4: 29–32.

64. D'eredita G, De-Leo-G, Punzo C et al. Timing of breast cancer surgery during menstrual cycle. A 10 year analysis of 133 premenopausal women. The Breast 1995; 4: 25–28.

65. Holli K, Isola J, Hakama M. Prognostic effect of timing of operation in relation to menstrual phase of breast cancer patient: fact of fallacy. Br J Cancer 1995; 71: 124–127.

66. Kurebayashi J, Sonoo H, Shimozuma K. Timing of surgery in relation to the menstrual cycle and its influence on the survival of Japanese women with operable breast cancer. Surg Today 1995; 25: 519–524.

67. Donegan W L, Hartz A J, Rimm A A. The association of body weight and recurrent cancer of the breast. Cancer 1978; 41: 1590–1594.

68. Senie R T, Rosen P P, Rhodes P et al. Obesity at diagnosis of breast cancer influences duration of disease free survival. Ann Intern Med 1992; 116: 26–32.

69. Vatten L J, Foss O P, Kvinnsland S. Overall survival of breast cancer in relation to preclinically determined total serum cholesterol, body mass index, height: a population based study. Eur J Cancer 1991; 27: 641–646.

70. Tartter P I, Papatestas A E, Ioannovich J et al. Cholesterol and obesity as prognostic factors in breast cancer. Cancer 1981; 47: 2222–2227.

71. Kyogoku S, Hirohata T, Takeshita S et al. Survival of breast cancer patients and body size indicators. Int J Cancer 1990; 46: 824–831.

72. Coates R J, Clarke W S, Eley J W et al. Race, nutritional status and survival from breast cancer. J Natl Cancer Inst 1990; 82: 1684–1692.

73. Newman S C, Miller A B, Howe G R. A study of the effect of weight and dietary fat on breast cancer survival. Am J Epidemiol 1986; 123: 767–774.

74. Zumoff B, Gorzynski G, Katz J L et al. Nonobesity at the time of mastectomy is highly predictive of 10 yr disease free survival in women with breast cancer. Anticancer Res 1982; 2: 59–62.

75. Boyd N F, Campbell J E, Germanson T et al. Body weight and prognosis in breast cancer. J Natl Cancer Inst 1981; 67: 785–789.

76. Lees A W, Jenkins H J, May C L et al. Risk factors and 10 year breast cancer survival in Northern Alberta. Breast Cancer Res Treat 1989; 13: 143–151.

77. Mohle-Boetani J C, Grosser S, Whittemore A S et al. Body size, reproductive factors and breast cancer survival. Pre Med 1988; 17: 634–642.

78. Hebert J R, Augustine A, Barone J et al. Weight, Height and body mass index in the prognosis of breast cancer: early results of prospective study. Int J Cancer 1988; 42: 315–318.

79. Eberlein T, Simon R, Fisher S, Lippman M E. Height, weight and risk of breast cancer relapse. Breast Cancer Res Treat 1985; 5: 81–86.

80. Katoh A, Watzlaf V J M, D'Amico F. An examination of obesity and breast cancer survival in postmenopausal women. Br J Cancer 1994; 70: 928–933.

81. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer 1991, 49: 526–530.

82. Jain M, Miller A B. Pre-morbid body size and the prognosis of breast cancer. Int J Cancer 1994; 59: 363–368.

83. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer, vol 1: Worldwide evidence 1985–1990. Oxford: Oxford University Press, 1990: 12–18.

84. Rochfort H, Augereau P, Briozzo P et al. Structure, function, regulation and clinical significance of the 52K pro-cathepsin-D secretion by breast cancer cells. Biochemie 1988; 70: 943–949.

85. Duffy M J, Reilly D, O'Sullivan C et al. uPA, a new and independent prognostic marker in breast cancer. Cancer Res 1990; 50: 6827–6829.

86. Hart I R, Woolley D E. Relationship between invasion and metastasis and role of proteaolytic enzymes. In: Mareel M M, Calman K C, eds. Invasion, experimental and clinical implications. Oxford: Oxford University Press, 1984: 63–78, 228–251.

87. Takeichi M. The cadherins: cell–cell adhesion molecules. Development 1988; 102: 639–655.

88. Moyer D L, Sahwi S E, McCauley D et al. In: Beller F K, Schuemacher G B R, eds. Cells of uterine fluid. Amsterdam: Elsvier, 1979: 59–71.

89. Sabourin J C, Martin A, Baruch J et al. bcl-2 expression in normal breast tissue during the menstrual cycle. Int J Cancer 1994; 59: 1–6.

90. Lippman M E, Dickson R B, Bats S et al. Autocrine and paracrine growth regulation of human breast cancer. Breast Cancer Res Treat 1986; 7: 59–70.

91. Lotzova E. Role of human circulating and tumour-infiltrating lymphocytes in cancer defense and treatment. Nat Immun Cell Growth Regul 1990; 9: 253–264.

92. Hanna W, Schnieder M. Enhancement of tumour metastasis and suppression of NK cell by beta-oestradiol treatment. J Immunol 1982; 130: 974–980.

93. Poutanen M, Moncharmont B, Vihko R. 17-beta hydroxy dehydrogenase gene expression in human breast cancer cells: regulation of expression by progestin. Cancer Res 1992; 52: 290–294.

94. Tyzzer E E. Factors in production and growth of tumour metastasis. J Med Res 1913; 28: 309–332.

95. Nissen-Myer R. Adjuvant cytostatic and endocrine therapy: increased cure rate or delayed manifest disease. Commentaries on Research in Breast Disease 1979; 1: 95–109.

96. Fisher E R, Turnbull R B. The cytological demonstration and significance of tumour cells in mesenteric venous blood in patients with colorectal cancer. Surg Gynecol Obstet 1955; 100: 102–108.

97. Hansen E, Norbert Wolff N, Knuechel R, Ruschoff J, Hofstaedter F, Taeger K. Tumor cells in blood shed from the surgical field. Arch Surg 1995; 130: 387–393.

98. McCulloch P, Choy A, Martin L. Association between tumour angiogenesis and tumour cell shedding into effluent venous blood during breast cancer surgery. Lancet 1995; 346: 1334–1335.