Unopposed oestrogen and survival of breast cancer

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SUMMARY. 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 < 0.000001), 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 < 0.000001). 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 Beatson1 and Mueller et al.2 This was resurrected by Ratajczak et al3 and Hrushesky et al4 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 al8 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
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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 (≤50 years) vs peri-postmenopausal (≥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. 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. 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.

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 (e.g. 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 prognostic 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 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. Two articles 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 were included for meta-analysis on age as a prognostic factor, 28 studies in 27 articles for timing of surgery, and 18 articles 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. 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 \( \chi^2 \) 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
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 and at least two other studies corroborate our finding.

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 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, 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 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). These two proteases bestow invasive potential on the primary tumour. The ability of the primary tumour to secrete these proteases has been inversely correlated with survival from breast cancer. 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 adhesion, the molecules which maintain the adhesive property of cells. 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. These two mechanisms of invasion and lack of adhesion can increase the metastatic potential of tumour cells. The disseminated tumour cells, when nested at distant sites, may be well supported for survival due to increased expression of bcl-2 oncogene preventing apoptosis and proliferation by growth factors under the oestrogen stimulus. The establishment of micrometastases is prevented by the natural host defence mechanism of natural killer (NK) cells. The NK cell activity is suppressed by circulating oestrogens, producing a permissive environment for development of micrometastases. 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.

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 and Nissen-Meyer. Malignant cells in the circulation at the time of surgery were first demonstrated by Fisher & Turnbull. 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. 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


