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Review

Timing of surgery during the menstrual cycle and prognosis of breast cancer

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There are conflicting reports on the differential effect of surgery performed during the two phases of the menstrual cycle, namely, follicular and luteal, and prognosis of operable breast cancer. A statistical meta-analysis of the published evidence suggests a modest survival benefit of 15 ± 4% when the operation is performed during the lueteal phase. Further research in this area might provide a novel avenue to understand the natural history of breast cancer. A spin off from these studies might be the understanding of the importance of events that occur at the time of surgery in determining long term prognosis.

1. Introduction

The menstrual cycle is a rhythmic preparation for extrusion of ovum and subsequent pregnancy if the ovum is fertilized. The events are under the influence of the hypothalamic gonadotrophins follicle stimulating hormone (FSH) and luteinizing hormone (LH) that regulate the release of sex steroid hormones estrogen and progesterone from the ovarian interstitium which in turn prime the ovarian follicles and induce ovulation (figure 1). Assuming that day 0 is the first day of menstrual flow of the last menstrual period, all hormones are low for the first 4–5 days. This is the early period of follicular development. Estrogens (ER) gradually rises for the next 3–4 days followed by a rapid peak by 12th day which is a day before the LH and FSH peak. Ovulation occurs 24–36 h after the LH peak by about the 14th day. The second peak of estrogen occurs about a week after ovulation and is opposed by a progesterone peak. In addition progesterone shows a small increase in concentration corresponding to the LH surge. Hence estrogens remains unopposed during the follicular phase, up to day 12 to be precise, and during the rest of the cycle progesterone opposes the effects of estrogen (Yen 1986).

2. The first reports

The timing of surgery during the menstrual cycle and breast cancer survival has been debated since the first report in the Lancet in 1989 by Hrushesky *et al* (1989). They reported on timing of surgery during the menstrual cycle in 41 women with operable breast cancer. Ten year survival was 95% for the 22 women who had their tumours excised during peri-ovulatory period (days 7–20) whereas it was 79% for the 19 women who had their tumours resected during peri-menstrual period (7 days on either side of the first day of the last menstrual period, days 0–6 and 21–36). Their selection of intervals was based on murine experiments reported earlier by the group. Ratajczak *et al* (1988) found that timing of resection of transplantable breast tumours within the murine estrous cycle determined the incidence of lung metastases and death of mice. Resection of tumour during proestrous phase had two and half times better survival compared to resection during metestrous phase. The proestrous phase is characterized by a surge in lueteinizing and follicle stimulating hormone with a background combination of progesterone and estrogen. This approximately corresponds to the peri-ovulatory period (7 days on either side of putative time of ovulation, days 7–20) in human menstrual cycle.

The hypothesis was subsequently redefined by Badwe *et al* (1991a) who suggested that resection of tumour during the phase of unopposed estrogen may be deleterious for survival. Badwe *et al* (1991a) compared survival of 75 women on whom surgery was performed during days 3–12 (unopposed estrogen phase) with 174 women who had resection during the remainder of the menstrual cycle (days

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0–2, 13–32, N = 174). The overall survival at 10 years was 54% for unopposed estrogen group compared to 84% for the other group ($P < 0{\cdot}001$). On multivariate analysis, the number of metastatic lymph nodes, timing of surgery, histological type and age were significant determinants of survival.

3. The hypothesis

'The timing of surgery during the menstrual cycle and survival in breast cancer' carries two distinct postulates. First, hormonal milieu in the host can modulate metastatic potential of breast cancer and second, events at the time of surgery can influence survival. It may be worthwhile examining the evidence for and against these postulates and then decide as to whether a prospective randomized study would be justified.

4. Hormones and breast cancer survival: Clinical evidence

A deleterious effect of unopposed estrogen on survival was deduced from poor survival in peri-menopausal women with breast cancer (Langlands *et al* 1979; Caleffi and Fentiman 1989; Badwe and Hawaldar 1994). Natural cessation of ovarian function is associated with repeated anovulatory cycles before a true post-menopausal state is reached. During these anovulatory cycles estrogen would be unopposed much more frequently, compared to pre-menopausal women. The unopposed estrogen in these women would still be much higher compared to that in post-menopausal women.

If unopposed estrogen is responsible for the deleterious impact on survival, then the effect should be evident whenever women experience this state. In pre-menopausal women during the follicular phase or days 3–12 of the menstrual cycle, estrogen is unopposed. A meta-analysis (using a fixed effect model) of all the published studies (Hrushesky *et al* 1989; Badwe *et al* 1991a, b; Goldhirsch *et al* 1991, 1997; Kurebayashi *et al* 1991; Low *et al* 1991; Powles *et al* 1991; Rageth *et al* 1991; Sainsbury *et al* 1991; Senie *et al* 1991; Stewart 1991; Ville *et al* 1991; Gnant *et al* 1992; Sigurdsson 1992; Callies 1993; Nathan *et al* 1993; Spratt *et al* 1993; Stonelake *et al* 1993; Wobbes *et al* 1993; Corder *et al* 1994; Engele *et al* 1994; Jager and Sauerbrei 1994; Kroman *et al* 1994; Saad *et al* 1994; Sauerbrei *et al* 1994; Veronesi *et al* 1994; D'eredita *et al* 1995; Holli *et al* 1995; von-Minckwitz *et al* 1995; Levine *et al* 1996; Martinez-Lacaci and Dickson 1996; Tsuchiya *et al* 1996; Chag *et al* 1997; Mondini Guido *et al* 1997; Vanek *et al* 1997; Zhang 1998) dealing with timing of surgery that allowed comparison of unopposed estrogenic phase versus opposed estrogenic phase, showed an odds reduction (OR) of 15% with confidence intervals ± 4 ($P = 0{\cdot}003$) (figure 2). The test for trend according to year of publication is not significant and test for heterogeneity is significant ($P < 0{\cdot}001$). Three (Ville *et al* 1991; Webbes *et al* 1993; Badwe *et al* 1994) of these studies have had circulating serum progesterone and estrogen measured a day or two on either side of the day of surgery. All three studies showed a protective effect of circulating progesterone on the event of metastasis and death. The overall effect was OR $52{\cdot}8 \pm 32\%$, $2P < 0{\cdot}001$ (test of heterogeneity and trend NS, $P > 0{\cdot}2$) (figure 3).

Peri-menopausal and post-menopausal women are more likely to have unopposed estrogen compared to pre-menopausal women. In pre-menopausal women at least 50% of the times estrogen will be opposed by progesterone. A meta-analysis of 22 published studies examined the effect of menopausal status or age at diagnosis on either side of 50 years (Badwe and Hawaldar 1991). Fifteen of the 22 studies revealed better survival in pre-menopausal (or < 50 years of age) and 7 showed equivocal results. The overall collated evidence showed a significantly higher survival in pre-menopausal women (OR 0·76, CI 0·74–0·78, $2P < 0{\cdot}0000001$) with an odds reduction of 24 ± 1% (figure 4).

In post-menopausal women, the source of estrogen is the enzyme aromatase in body fat which converts precursors of estrogen into active hormone (Grodin *et al* 1973). Obese women produce more estrogen than thin women (Trichopoulos *et al* 1987) hence if unopposed estrogen is deleterious for survival, thin women should experience a better survival than obese women with breast cancer. A meta-analysis of eighteen studies (Badwe and Hawaldar 1991) addressing obesity and breast cancer survival supported a quantitative inverse relationship between them. In 12 studies non-obese women had better survival compared to obese women whereas 6 studies showed equivocal results. None of the studies had obese women with better survival in comparison to thin women. The OR for thin women was $36{\cdot}6 \pm 3{\cdot}7$, $2P < 0{\cdot}000001$ (figure 5).

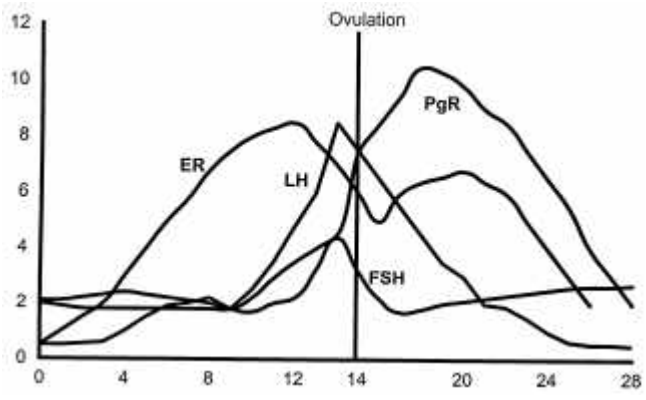

Figure 1. Variations in steroid sex hormones during the menstrual cycle.

5. Hormones and breast cancer survival: Laboratory evidence

Metastasis is a cascade of sequential steps involving multiple tumour host interactions. Successful metastasis involves migration of tumour cells from its primary organ to a distant site in adequate numbers to establish a colony. The first process of migration requires digestion of surrounding tissue by tumour cells to gain access to lymphatic and blood vessels. Proteases bestow this invasive ability upon tumour cells. There are at least two proteases that are known to be modulated by estrogen *in vitro*. Cathepsins (Rachfort *et al* 1988) and uPA (Saksela and Rifkin 1988) are up-regulated in breast cancer cells by estrogen and the ability of the primary tumour to secrete these two proteases has had inverse correlation to survival in breast cancer (Rachfort *et al* 1988; Janicke *et al* 1989). Saad *et al* (1998) recently reported increased expression of cathepsin L, matrix metalloproteinase (MMP-9 and MMP-2) and down regulation of tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2 in tumours excised during the follicular phase of the menstrual cycle. The invasive ability of the primary tumour was pathologically evaluated by the presence of vascular and lymphatic invasion (LVI). The incidence of LVI has been found to strongly correlate with unopposed estrogenic phase in premenopausal women (Badwe *et al* 1995) and has a direct relation with obesity as assessed by body weight (Badwe *et al* 1997). Tumour cells under the influence of estrogen could secrete proteases thus increasing their invasive ability. The products of digestion by protease would usurp ionic calcium due to pH changes which in turn would reduce the binding capacity of E cadherin (calcium dependent) (Takeichi 1988). This would allow cells to migrate to gain access to lymphatic and vascular channels to be carried to distant sites. There are many other prognostic factors of operable breast cancer that have been shown to be modulated unfavourably by estrogen. These include EGF (Marques and Franco 1993) and Cyclin D (Altucci *et al* 1996) that can induce proliferation of tumour cells and allow them to nestle at distant sites. It is not only that tumours manifest increased ability to invade and proliferate but the host environment is also permissive under the

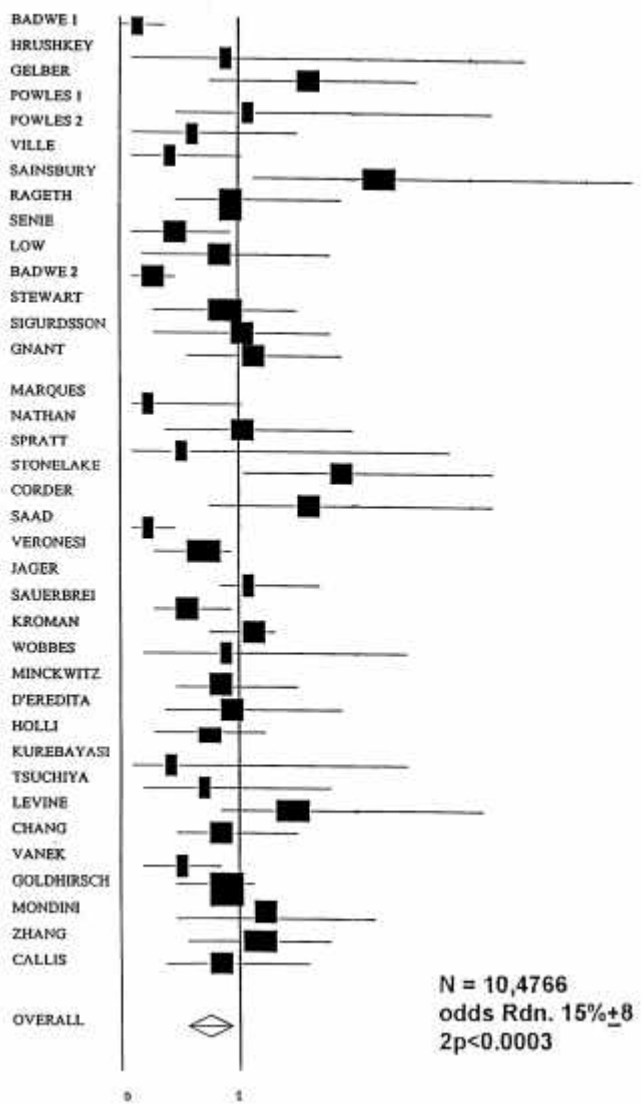

Figure 2. Meta-analysis of studies on timing of surgery during the menstrual cycle and survival in breast cancer. A square and horizontal line demarcate each study. The square represents the size and the event rate in the study. The horizontal line indicates 95% confidence limits. A study depicted to the left of unity (< 1) suggests superior outcome in women who had surgery during the luteal phase whereas that to the right of unity (> 1) indicates superior outcome in women who had surgery during the follicular phase. The diamond at the bottom indicates the overall effect which is odds reduction of 15 ± 8% in favour of women who had surgery during the luteal phase of the menstrual cycle.

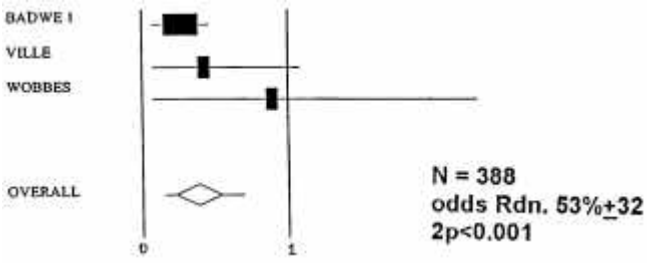

Figure 3. Meta-analysis of studies that measured serum progesterone levels at the time of surgery and survival in breast cancer. A square and horizontal line demarcate each study. The square represents the size and the event rate in the study. The horizontal line indicates 95% confidence limits. A study depicted to the left of unity (< 1) suggests superior outcome in women who had surgery when progesterone levels were > 5 ng/ml whereas that to the right of unity (> 1) indicates superior outcome in women who had surgery when progesterone levels were < 5 ng/ml. The diamond at the bottom indicates the overall effect which is odds reduction of 52·8% in favour of women who had surgery during the luteal phase of the menstrual cycle.

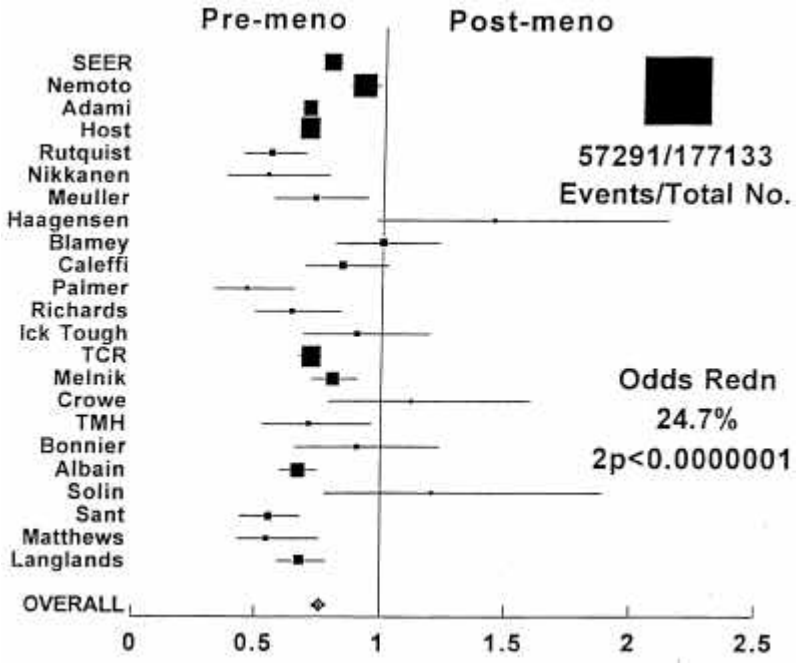

Figure 4. Meta-analysis of menopausal status and survival in breast cancer. A square and horizontal line demarcate each study. The square represents the size and the event rate in the study. The horizontal line indicates 95% confidence limits. A study depicted to the left of unity (< 1) suggests superior outcome in pre-menopausal women whereas that to the right of unity (> 1) indicates superior outcome in post-menopausal women. The diamond at the bottom indicates the overall effect which is odds reduction of 24·7 ± 1% in favour of pre-menopausal women with breast cancer.

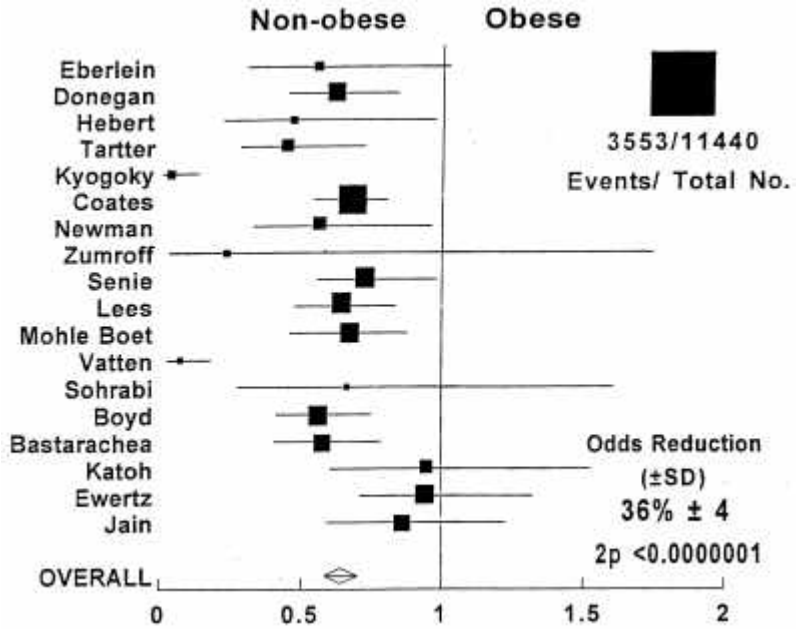

Figure 5. Meta-analysis of obesity and survival in breast cancer. A square and horizontal line demarcate each study. The square represents the size and the event rate in the study. The horizontal line indicates 95% confidence limits. A study depicted to the left of unity (< 1) suggests superior outcome in non-obese women whereas that to the right of unity (> 1) indicates superior outcome in obese women. The diamond at the bottom indicates the overall effect which is odds reduction of 36·6 ± 3·7% in favour of non-obese women with breast cancer.

unopposed estrogenic influence. The NK cell activity is at its lowest ebb during the follicular phase (Hanna and Schnieder 1982).

6. Events at the time of surgery and survival: Clinical evidence

That the hormonal milieu during the menstrual cycle might influence prognosis leads to the assumption that events at the time of surgery are implicated in the long term survival of breast cancer. Data from randomized trials (Badwe and Vaidya 1996), modelling studies (Baum and Badwe 1994), and the laboratory suggest that the event of surgery influences the onset or autonomy of distant micrometastases. In sharp contrast to rigorous testing that have been undertaken for radiation and chemotherapy in randomized trials [Early Breast Trialist' Collaborative Group (EBCTCG) 1990], the effect of surgery on survival has never been tested. The best experiment to test surgical dissemination/autonomy (SDA) hypothesis would be to compare surgery versus no surgery; but such a trial would be unethical.

Randomized trials of screening offer the next best opportunity to test the SDA hypothesis. In these trials the event of surgery is delayed in the control group by about 18–24 months (lead-time) as compared to screened group; hence the first few years of follow up should offer a comparison between surgery versus natural progression *in vivo*. As the majority of cases undergo surgery eventually in either arm, a comparison between early surgery versus late surgery can be made. The conventional theory (Fisher 1977) holds that surgery as an event does not influence the natural history of cancer, and survival is determined by the presence of micrometastases prior to diagnosis. The conventional theory would predict identical number of deaths in both the groups for the first few years. On the other hand, if dissemination/autonomy were to occur at the time of surgery it would lead to excess deaths in screened group for the first few years. A meta-analysis (Elwood *et al* 1993) of annual cumulative mortality of all the published screening trials in breast cancer revealed that there was indeed an excess mortality in the screened group in the first few years. In women above the age of 50 years the excess mortality in the screened group was seen only in the first year whereas in younger women it persisted for the first 7 years after randomization (table 1). An excess mortality in the screened group was evident in both the randomized trials of screening for lung cancer (Fontana 1985 and Kubik *et al* 1990) beyond 6 years of follow up. In colon cancer screening trial (Mandel *et al* 1993), the group that had biennial screening for occult blood in stool, experienced excess deaths as compared to control group for the first 10 years. Thus all the published screening data suggest that early intervention in the form of surgery had a detrimental effect on the natural history of cancer in the first few years. A careful analysis of the breast cancer screening data reveals that the ultimate reduction in deaths due to breast cancer is the net effect of early excess mortality in the screened group (a comparison of surgery vs no surgery) and later saving of lives (a comparison of early surgery vs late surgery).

Table 1. Meta-analysis of data from screening trials for breast cancer (Elwood *et al* 1993).

Years after randomization	Ratio of average cumulative mortality: Screened/control	
	Age < 50 yr	Age > 50 yr
1	1·67	1·62
2	1·05	0·69
3	1·88	0·76
4	1·31	0·77
5	1·22	0·66
6	1·15	0·65
7	1·02	0·69
8	0·98	0·67
9	0·92	0·67
10	0·90	0·68

Ratio of cumulative mortality in screening vs control by years of randomization showing excess deaths in screened group up to 7th year in women < 50 years and for the first year in women > 50 years.

7. Events at the time of surgery and survival: Laboratory evidence

Laboratory evidence for surgical dissemination has been available since the beginning of this century. Tyzzer (1913) showed it in animal studies, Fisher and Turnbull (1955) in portal vein blood samples in colon cancer and recently with greater precision of PCR technology dissemination has been demonstrated in prostate (Eschwege *et al* 1995) and breast cancer (Brown *et al* 1994). Fisher *et al* (1989) from animal experiments suggest outgrowth of metastasis after the event of surgery and postulate that it may be related to perturbation of balance between inhibitory and stimulatory factors elaborated by the primary tumour. Holmgren *et al* (1995) showed that the removal of a primary Lewis lung carcinoma tumour in mice resulted in the exponential growth of its lung metastases. The presence of primary tumour elaborating angiostatin which had anti-angiogenic property suppressed outgrowth of micro-metastases.

8. Conclusion

Deleterious effect of unopposed estrogen at the time of surgery suggests that events at the time of surgery can influence the long-term survival in breast cancer. It leads one to explore the effect of surgery on the natural history of breast cancer. It will be impossible to test this postulate as a trial of surgery vs no surgery will be unethical. The best opportunity to compare surgery vs no surgery is early years

of screening trial data. It is not surprising that all screening trials (13 in all) have shown early excess mortality (breast, lung, colon and now prostate).

There is enough evidence to support both the hormonal influence as well as SDA hypothesis. It is tempting to draw a simile between the effect of observer on the observed in quantum physics and SDA model in breast cancer. The SDA model suggests that event of diagnosis and treatment of the primary tumour changes its behaviour. The SDA model, induces a radical shift in the understanding of breast cancer biology and offers opportunities to try modifiers of biological potential for metastasis (e.g., tamoxifen, progesterone, anti-protease, angiostatin) in neo-adjuvant setting and continues to support beneficial effects of early detection and surgery in the natural history of disease.

It would be worthwhile to plan a trial comparing standard practice (unplanned surgery as patient enrolls) versus surgery during the luteal phase in pre-menopausal women. Another possibility, based on circulating progesterone studies, would be to compare primary progesterone treatment (4–10 days prior to surgery) with standard practice. Such a primary progesterone trial is already underway and is conducted by the Indian Breast Group. Over 200 patients have so far been accrued. The details of the trial would be available from Clinical Research Secretariat, Tata Memorial Centre, Parel, Mumbai, India (Email: tmhcrs@vsnl.com).

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