Timing of breast cancer surgery during the menstrual cycle-is there an optimal time of the month? (Review)

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Abstract. An intriguing relationship between menstrual cycle phase at the time of breast cancer surgery and clinical outcomes was first proposed in the late 1980s. Despite a number of clinical studies conducted to address this, as well as meta-analyses and systematic reviews, there remains significant controversy surrounding the effect of menstrual cycle phase at time of surgery on the prognosis of premenopausal breast cancer. While some studies have suggested that surgery performed during the luteal phase results in the most favourable outcome, other studies report the follicular phase is more favourable, and others show no association. Given the conflicting results, there remains insufficient evidence to determine whether there is an optimal time of the month to perform surgery. This issue has dogged breast cancer surgery for decades; knowledge of an optimal time of the month to conduct surgery would be a simple approach to improving patient outcomes. This review explores the potential biological mechanisms through which the hormonal milieu might contribute to differences in prognosis, and why clinical findings are so variable. It is concluded that a significant problem with current clinical research is the lack of insight from mechanistic studies. While there are a number of plausible biological mechanisms that could lead to altered survival, supporting evidence is limited. There are also variable approaches to defining the menstrual cycle phase and hormone receptor status of the tumour and few studies controlled for prognostic factors such as tumour size and stage, or addressed the impact of adjuvant treatments. Elucidation of the specific confounding factors, as well as biological mechanistic pathways that could explain the potential relationship between timing of surgery and survival, will greatly assist in designing robust well-controlled prospective clinical studies to evaluate this paradigm.

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Contents

1. Introduction

In premenopausal women, fluctuations in circulating estrogen and progesterone occur across the course of the menstrual cycle. Breast tissue is highly responsive to ovarian hormones, and the cellular and molecular changes that occur in the breast over the course of the menstrual cycle affect breast development and function (1,2). These hormones also affect the activity of breast cancer cells, both directly through ligand-receptor binding to hormone receptor positive cancer cells, and indirectly through effects on cells within the cancer cell microenvironment (3). An intriguing association between the timing of surgery in relation to menstrual cycle phase and breast cancer clinical outcomes was first proposed in the late 1980s (4,5). This concept provides a potential new approach to improving survival outcomes for premenopausal women. If the hormone milieu at a specific phase of the menstrual cycle results in a more favourable outcome, then the timing of breast cancer surgery to this phase might be a non-toxic and cost-effective means of reducing morbidity and mortality for young breast cancer patients. However, there is

significant controversy in the literature surrounding the impact of menstrual cycle phase at the time of surgery on breast cancer outcomes.

Here, we review the current evidence for a relationship between the menstrual cycle phase at the time of surgery on breast cancer outcomes, and explore the biological mechanisms that may contribute to a phase-specific prognosis. Relevant articles were identified by searching the PubMed database for clinical studies investigating the impact of menstrual cycle stage at the time of breast cancer surgery on patient survival outcomes, and also by reviewing the reference lists of relevant articles. All studies with the full text available on The University of Adelaide or SA Health Library databases were included in the review.

Mouse studies supported by small retrospective clinical studies suggested that changes in the characteristics of the tumour and tumour microenvironment across the menstrual cycle might influence the metastatic potential of tumour cells, and affect clinical outcomes in premenopausal women. However, while some studies suggest that surgery performed during the luteal phase results in favourable outcomes in terms of metastatic incidence, disease free survival, and overall survival (6-14), other studies report the follicular phase is more favourable (5,15,16), and other studies show no association (17-24).

We conclude that currently, there is insufficient evidence to support a change in surgery scheduling for premenopausal breast cancer patients. The lack of consistency in studies is likely due to a number of differences in study design and the small sample sizes used. There are variable approaches to defining the menstrual cycle phase and hormone receptor status of the tumour. Few studies controlled for prognostic factors such as tumour size and stage, or addressed the impact of adjuvant treatments such as chemotherapy and hormonal therapy. There are a number of potential biological mechanisms that might affect surgical outcomes (Fig. 1), but currently no causal mechanisms have been demonstrated. To fully address this lack of clear evidence, prospective, well-controlled studies are required, supported by research on animal models that link biological mechanisms with clinical findings.

2. Impact of ovarian cycle phase at the time of surgery on mammary cancer metastasis in rodent models

In 1988, Ratajczak *et al* (4) published a study showing a relationship between the incidence of postoperative pulmonary metastasis, and the rodent estrous cycle phase at which the mammary tumour was removed. Using a hormone receptor-positive murine mammary carcinoma, the authors showed that tumours resected from mice around the time of ovulation (designated 'near estrus') showed fewer incidences of pulmonary metastasis 4 weeks after surgery compared to tumours resected at a time further away from the time of ovulation (designated 'post-estrus'). The study used the cytology of vaginal smears to classify the phases of the estrous cycle and did not assess circulating ovarian hormones in the mice. However, this classification system would have resulted in the mice exhibiting high circulating concentration of estrogen and low progesterone at 'near estrus', and high circulating concentration of progesterone and mid-range estrogen at 'post-estrus'. The authors demonstrated that the incidence of lung metastasis, as assessed by gross morphology and bioassay, was significantly reduced in 'near estrus' mice (44 of 60 mice; 73%) compared to 'post-estrus' mice (64 of 78 mice; 82%).

The authors proposed that the hormonal environment at the time of surgery can influence the metastatic potential of a cancer cell, through direct effects on the tumour, or indirect effects on the cancer microenvironment or the host immune system. Different hormonal environments may either facilitate or impede the metastasis of breast cancer cells, and therefore explain the observed differences in pulmonary metastasis with estrous cycle phase.

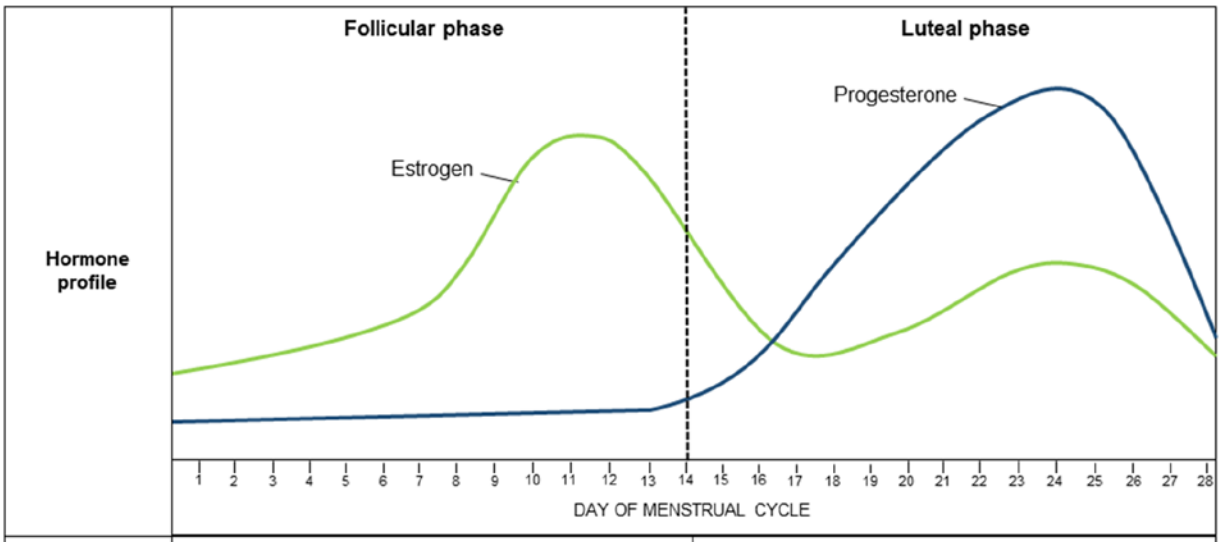
However, a subsequent study by Ben-Eliyahu *et al* (25) suggested that rats are instead more susceptible to mammary carcinoma metastasis during the proestrus phase of the estrous cycle. The authors investigated lung metastasis in rats injected intravenously with hormone receptor-negative cancer cells, and reported that metestrus and diestrus stages of the cycle, which are characterised by high circulating concentrations of progesterone and mid-range estrogen, were protective against metastasis. Similarly, the authors demonstrated that treatment with estrogen increased the metastatic burden in the lung, an effect which was attenuated by progesterone treatment (25).

The current evidence in animal models supports the possibility that estrous cycle stage influences the risk of tumour metastasis. However, given the conflicting results, it remains unclear which stage of the estrous cycle may provide a more favourable prognosis, and there is no clear understanding of the underlying biological mechanisms which may contribute to these phase-specific differences in outcomes.

3. Clinical evidence of an impact of menstrual cycle phase at time of surgery on breast cancer metastasis

In 1989, Hrushesky *et al* (5) published the first retrospective review in premenopausal women, investigating the effects of the timing of breast cancer surgery on disease recurrence and metastasis. The review included 44 premenopausal women, with both hormone receptor-positive and -negative disease. The authors found that patient outcomes varied significantly depending on the day of the menstrual cycle that surgery was performed. In agreement with their earlier mouse study, the authors found that women operated on close to the time of menstruation showed poorer disease free and overall survival outcomes, and a greater incidence of metastasis, compared to women operated on during other phases of the cycle. This suggests that premenopausal women might have an increased risk of metastasis and poorer survival outcomes if surgery is performed during the perimenstrual phase of their menstrual cycle.

However, later studies have found conflicting results (26,27), and there is significant controversy in the literature surrounding the effects of the menstrual cycle stage at the time of surgery on the survival outcomes of premenopausal breast cancers. In agreement with animal studies published by Ben-Eliyahu *et al* (25), several studies in premenopausal women have reported favourable outcomes for women when surgery is performed during the perimenstrual phase of their menstrual cycle (26,27). These findings are in direct disagreement with those reported by Ratajczak *et al* (4) and point to the complexities of experimental design in affecting results.



Biomarker profile	↑ ER positivity, ↑ hormone-driven tumour proliferation	↑ EGFR expression, ↑ HER2 expression, ↑ growth factor-driven tumour proliferation
Tumour cell dissemination	↑ incidence of vascular invasion, ↑ VEGF expression, ↑ expression of EMT-associated genes ↓ E-caderin expression	↓ incidence of vascular invasion, ↓ VEGF expression,
Immune profile	↑ proinflammatory cytokines (CSF1, CFS2, IFNG, TNFA) ↑ IGF1, ↓ macrophage abundance, ↑ Treg abundance, ↓ NK abundance and activity ↓ IL-2 production, ↑ gut microbiome diversity	↓ proinflammatory cytokines, ↑ macrophage abundance, ↓ Treg abundance, ↑ NK abundance and activity ↑ IL-2 production

Figure 1. Summary of the biological mechanisms that could affect the metastatic ability of breast cancer cells and contribute to a phase-specific prognosis. The effects of estrogen (green) and progesterone (blue) on breast cancer biomarker expression, tumour cell dissemination and immune function. ER, estrogen receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor recpetor-2; VEGF, vascular endothelial growth factor; EMT, epithelial-to-mesenchymal transition; CSF, colony-stimulating factor; IFNG, interferon γ; TNF-α, tumour necrosis factor α; IGF1, Insulin-like growth factor-1.

A meta-analysis of 37 published studies (n=10,476) suggested favourable prognosis when surgery was performed during the luteal phase (28). Similarly, a meta-analysis of 5353 premenopausal women demonstrated an overall survival benefit for women operated on during the luteal phase of the menstrual cycle (29). Conversely, two meta-analyses of 19 published studies (30,31), found no significant relationship between menstrual cycle stage and patient prognosis.

The discrepancies between meta-analyses are likely associated with differences in their methodology. Different meta-analyses had different defining criteria for study inclusion; restricting their analysis to studies based on only one specific type of menstrual cycle stage classification, using one combined prognostic outcome, or limiting analysis to cohorts of women residing solely in Italy (30) or the United States (29). The four systematic reviews to date (31-34), which examined the relationship between the menstrual cycle stage at the time of surgery and patient outcomes, reported that there is insufficient evidence to determine if one phase of the menstrual cycle provides a more favourable outcome.

4. Confounding factors that could affect the relationship between timing of surgery and prognosis

Despite the large number of existing studies, there remains significant controversy in the literature surrounding how the menstrual cycle stage at time of surgery affects breast cancer outcomes. Disagreement between published studies could be due to a number of confounding factors including how menstrual cycle stage was classified for the study, variability in circulating hormone profiles between women, tumour stage at the time of surgery, and how psychological stress can affect ovarian hormone secretion and menstrual cycling.

Differences in classification methods can introduce significant variability into results, and may provide some explanation for the differences in results between different studies (5-24,26,27) (Table I). Other factors include inaccuracies in menstrual cycle data, as there can be significant variability in cycle length (i.e., 22-36 days) between women (35); and other factors, such as irregular menses, use of oral contraceptives, recent pregnancies, or differing hormonal and chemotherapy treatment regimens may impact circulating ovarian hormones and menstrual cycle phase. McGuire *et al* suggested that by changing the cut-off days used to classify the menstrual cycle phase, a significant number of patients can be shifted into a different phase, and this could influence the significance and outcomes of published results (36,37).

Differences in the definition of surgery could also contribute to discordances between findings (Table II). The majority of studies that found an association between menstrual cycle stage at the time of surgery and patient prognosis defined surgery as the time of first intervention. It is possible that the menstrual cycle stage when the tumour is first manipulated, through excision or incision biopsies or fine needle aspiration (FNA) has the greatest effect on patient prognosis, regardless of the total number of surgeries. Indeed, a study by Corder *et al*

Table I. Methods for classifying the menstrual cycle stage.

Author	Number of women	Favourable outcome	Variable measured	Classification of menstrual cycle using serum hormone concentrations			Classification of menstrual cycle using patient reported last menstrual period			
				Follicular	Luteal	Ovulatory	Follicular	Luteal	Midcycle	Perimenstrual
Hrushesky *et al* (5)	44	Follicular	DFS, OS	-	-	-	-	-	7-20	0-6, 21-32
Senie *et al* (6)	283	Luteal	DFS	-	-	-	0-14	>14	7-20	0-6, 21-32
Badwe *et al* (7)	249	Luteal	DFS, OS	-	-	-	3-12	13-32, 0-2	-	-
Wobbes *et al* (17)	89	No relationship	DFS	E2 100-990 pmol/l, P4<1.3 nmol/l	E2 330-1,500 pmol/l, P4 14-81 nmol/l	E2 86-1,700 pmol/l, P4 1.5-9.7 nmol/l	0-9	13-24	10-12	-
Badwe *et al* (18)	271	No relationship	DFS, OS	P4<1.5 ng/ml	P4>1.5 ng/ml	-	3-12	13-28, 0-2	-	-
Corder *et al* (15)	157	Follicular	DFS, OS	-	-	-	3-12	0-2, 13-32	-	-
Veronesi *et al* (8)	1,175	Luteal	DFS	-	-	-	0-14	15-36	-	-
Saad *et al* (10)	84	Luteal	DFS, OS	-	-	-	1-12	>12	-	-
Saad *et al* (9)	96	Luteal	DFS, OS	-	-	-	1-12	>12	-	-
Minckwitz *et al* (11)	266	Luteal	DFS, OS	-	-	-	3-12	13-35, 0-2	-	-
Holli *et al* (19)	267	No relationship	OS	-	-	-	1-14	15-28	-	-
Mohr *et al* (12)	289	Luteal	DFS, OS	P4<4 ng/ml	P4>4 ng/ml		0-12	13-30	-	-
Vanek *et al* (27)	150	Perimenstrual	DFS, OS	-	-	-	-	-	7-20	0-6, 21-32
Milella *et al* (14)	248	Luteal	DFS, OS	-	-	-	0-14	15-37	-	-
Nomura *et al* (23)	721	No relationship	DFS, OS	-	-	-	3-12 or 0-14	0-2, 13-32 or 15-36	-	-
Holmburg *et al* (24)	774	No relationship	OS	E2<440 pmol/l	200-700 pmol/l	500-1300 pmol/l	-	-	-	-
Pujol *et al* (22)	360	No relationship	DFS, OS	P42.5 ng/ml, E2<100 pmol/l and LH<10 mIU/ml	P4>2.5 ng/ml	E2100 pg/ml, 10 mIU/ml	-	-	-	-
Takeda *et al* (26)	28	Perimenstrual	DFS	-	-	-	3-12 or 0-14	13-28, 0-2 or 15 -36	7-20	0-6, 21-32
Thorpe *et al* (21)	412	No relationship	DFS, OS	Not defined	Not defined	Not defined	0-14 or 3-12	15-36 or 0-12, 13-12	-	-
Grant *et al* (20)	834	No relationship	DFS, OS	P4<3 ng/ml	P4>5 ng/ml	-	0-21	21-35	-	-

Table I. Continued.

Author	Num ber of women	Favourable outcome	Variable measured	Classification of menstrual cycle using serum hormone concentrations			Classification of menstrual cycle using patient reported last menstrual period			
				Follicular	Luteal	Ovulatory	Follicular	Luteal	Midcycle	Perimenstrual
Kucuk *et al* (13)	90	Luteal	DFS, OS	P4<2.5 ng/ml, E2<100 pmol/l and LH<10 mIU/ml	P4 >2.5 ng/ml	E2>100 pmol/l, 10 mIU/ml	0-14	15-28	-	-
Liu *et al* (16)	554	Follicular	DFS, OS	-	-	-	1-14	15-31	-	-

Studies were identified by searching the PubMed database and were included if the full text were available on The University of Adelaide or salus SA Health Library databases. Menstrual cycle stage classification was based on either serum hormone concentrations, days since the patients last menstrual period, or both. DFS, disease free survival; OS, overall survival; E2, estrogen; P4, progesterone.

(1994) (15) reported that FNAs performed during the follicular phase were associated with an improved patient prognosis, but there was no association between menstrual cycle stage at the time of first surgical intervention and patient prognosis. On the other hand, Vanek *et al* (1997) (27) found that the menstrual cycle stage at the time of both biopsy and surgery correlated with patient disease free survival, suggesting that any time the tumour is manipulated, through either biopsies or surgeries, might influence patient prognosis.

To date, the majority of human studies have suggested that menstrual cycle stage at the time of surgery does indeed affect breast cancer outcomes; however, have disagreed on what stage of the cycle is optimal. It is unclear whether these observed effects of menstrual cycling are due to menstrual cycle phase per se, or due to biological effects of circulating hormones on breast cancer metastasis. Serum concentrations of estrogen and progesterone vary significantly between women of the same menstrual cycle stage. There is evidence that it is the elevated concentration of circulating progesterone during the luteal phase that exerts a protective effect against metastatic incidence (12,18). If favourable outcomes are associated with higher concentration of circulating progesterone, then treatment with progesterone prior to surgery may be a feasible approach to improving breast cancer outcomes. Indeed, it has been reported that the injection of hydroxyprogesterone prior to surgery is associated with improved disease free survival for node positive breast cancer patients (38). However, there is controversy in the literature on the beneficial effects of progesterone on prognosis, and not all studies found a beneficial relationship between progesterone concentrations and survival outcomes (22).

Alternatively, it may be that high luteinsing hormone (LH) or follicle-stimulating hormone (FSH) concentrations, which peak prior to ovulation, are responsible for poorer rates of disease free and overall survival independent of estrogen and progesterone concentrations. FSH and LH can increase the invasive ability of breast cancer cells *in vitro* and *in vivo* (39,40); and in breast cancer patients LH expression is increased in breast tumour tissue compared to normal breast tissue (41). However, the roles of LH and FSH in breast cancer initiation and progression are not well defined, and how they may contribute to metastasis warrants further investigation.

Several studies have shown that the effects of the menstrual cycle phase at the time of surgery on prognosis is more pronounced in lymph node positive patients (Table III). Lymph node positive tumours operated on during the luteal phase (6-8,11), or when circulating concentrations of progesterone were high (12,18), showed improved survival outcomes; however, these differences were less pronounced, or not observed, in node negative tumours. The more pronounced effect may be due to lymph node positive tumours already showing the potential for metastasis, and the hormonal environment at the time of surgery may further facilitate tumour cell metastasis in lymph node positive disease. However, not all studies have found a relationship between menstrual cycle phase and outcomes in lymph node positive patients (17,42).

Another confounding factor in these studies may be the acute psychological impact of a breast cancer diagnosis on ovarian hormones and menstrual cycle length. Stressful life events affect the hypothalamo-pituitary-ovarian axis through

Table II. Criteria in studies investigating the relationship between menstrual cycle stage and patient prognosis.

Author	Number of women	Favourable outcome	Variable measured	Surgery definition
Hrushesky *et al* (5)	44	Follicular	DFS, OS	First intervention
Senie *et al* (6)	283	Luteal	DFS	First surgical intervention
Badwe *et al* (7)	249	Luteal[a]	DFS, OS	First intervention
Wobbes *et al* (17)	89	No relationship[a]	DFS	First surgical intervention
Badwe *et al* (18)	271	No relationship[a]	DFS, OS	First surgical intervention
Corder *et al* (15)	157	Follicular	DFS, OS	Analysed both initial and definitive procedures
Veronesi *et al* (8)	1,175	Luteal	DFS	Definitive surgery
Saad *et al* (10)	84	Luteal	DFS, OS	First surgical intervention
Saad *et al* (9)	96	Luteal	DFS, OS	Analysed both initial and definitive procedures
Minckwitz *et al* (11)	266	Luteal	DFS, OS	First surgical intervention
Holli *et al* (19)	267	No relationship	OS	Undefined
Mohr *et al* (12)	289	Luteal[a]	DFS, OS	First intervention
Vanek *et al* (27)	150	Perimenstrual	DFS, OS	Analysed both initial and definitive procedures
Milella *et al* (14)	248	Luteal	DFS, OS	Definitive surgery
Nomura *et al* (23)	721	No relationship	DFS, OS	Definitive surgery
Holmburg *et al* (24)	774	No relationship[a]	OS	Definitive surgery
Pujol *et al* (22)	360	No relationship	DFS, OS	First intervention
Takeda *et al* (26)	28	Perimenstrual[a]	DFS	First surgical intervention
Thorpe *et al* (21)	412	No relationship	DFS, OS	First surgical intervention
Grant *et al* (20)	834	No relationship	DFS, OS	First surgical intervention
Kucuk *et al* (13)	90	Luteal	DFS, OS	First surgical intervention
Liu *et al* (16)	554	Follicular	DFS, OS	Undefined

The survival outcomes measured for each study are highlighted. Surgery was defined as either the first intervention (i.e., FNAs or biopsies), the first surgical intervention (i.e., excisional or incisional biopsies, breast conserving surgery, partial mastectomies or mastectomies), or the definitive surgery (i.e., re-excisions, mastectomies or axillary node dissections). In many cases, the date of first surgical intervention corresponded with the date of definitive surgery. All studies included malignant disease only, while some studies only included [a]invasive disease. DFS, disease free survival; OS, overall survival.

catecholamine-induced inhibition of gonadotropin-releasing hormone, suppressing ovulation and progesterone secretion (43). The impact of stress on circulating estrogen, progesterone and menstrual cycle length (44) is difficult to address in retrospective studies on timing of surgery with menstrual cycle phase.

5. Impact of menstrual cycle phase at time of surgery on adjuvant therapy

Hormone receptor expression in breast cancer directs decision-making around use of adjuvant therapies, and influences the extent to which a tumour responds to treatment. The majority of studies investigating the effect of cycle phase on breast cancer outcomes did not take into account the percent positivity of hormone receptors (Table IV), nor the treatment regimen given to patients (Table V). However, as hormone receptor expression and adjuvant therapy use are independent predictors of improved survival, differences in treatment regimens and treatment responses between menstrual cycle phases could confound results if not accounted for.

Breast cancer hormone receptor expression fluctuates across the menstrual cycle. Breast cancer tissue samples are more likely to be estrogen receptor (ER) positive, and exhibit greater ER positivity when taken during the follicular phase compared to the luteal phase (22,45). Furthermore, breast cancer samples exhibit greater progesterone receptor (PR) positivity during the ovulatory phase, compared to either follicular or luteal phases (22). The percentage of ER and PR positive cells in a tumour is a predictor of the response to therapy, where increasing hormone receptor expression is associated with an increased benefit to endocrine therapy (46,47).

Table III. Nodal status of patients involved in studies which examined the relationship between menstrual cycle stage and patient prognosis.

			Nodal status		
Author	Number	Favourable outcome	Pos	Neg	Ukn
Hrushesky *et al* (5)	44	Follicular	16	28	0
Senie *et al* (6)	283	Luteal[a]	117	166	0
Badwe *et al* (7)	249	Luteal[a]	126	123	0
Wobbes *et al* (17)	89	No relationship	46	39	4
Badwe *et al* (18)	271	No relationship	119	151	1
Corder *et al* (15)	157	Follicular	66	91	0
Veronesi *et al* (8)	1,175	Luteal[a]	436	739	0
Saad *et al* (10)	84	Luteal	45	39	0
Saad *et al* (9)	96	Luteal[b]	50	46	0
Minckwitz *et al* (11)	266	Luteal[a]	146	120	0
Holli *et al* (19)	267	No relationship	78	89	100
Mohr *et al* (12)	289	Luteal[b]	140	149	0
Vanek *et al* (27)	150	Perimenstrual	59	80	11
Milella *et al* (14)	248	Luteal	155	93	0
Nomura *et al* (23)	721	No relationship	329	392	0
Holmburg *et al* (24)	774	No relationship	-	-	-
Pujol *et al* (22)	360	No relationship	137	220	3
Takeda *et al* (26)	28	Perimenstrual	15	13	0
Thorpe *et al* (21)	412	No relationship	208	193	11
Grant *et al* (20)	834	No relationship	328	500	6
Kucuk *et al* (13)	90	Luteal	44	46	0
Liu *et al* (16)	554	Follicular	214	340	0

[a]Studies where the effect more pronounced in lymph node positive cases; [b]studies where the effect was limited to lymph node positive cases; -, nodal status was not stated; Pos, positive; Neg, negative; Ukn, Unknown.

Changes in hormone receptor expression with menstrual cycle phase might therefore affect the extent to which the tumour responds to treatment.

Similarly, growth factor receptor expression also fluctuates across the course of the menstrual cycle, and could contribute to a phase-specific prognosis. Increased expression of the epidermal growth factor receptor (EGFR) and human epidermal growth factor recpetor-2 (HER2) is observed during the follicular phase of the menstrual cycle (48,49), and has been associated with increased metastasis and poorer survival outcomes (50,51). Increased signalling through growth factor receptors during the follicular phase could promote breast cancer cell survival, facilitate metastasis, and contribute to the poorer outcomes observed during the follicular phase. However, other studies have instead suggested that EGFR and HER2 expression is highest during the luteal phase in the normal breast (52), and that its expression is inversely related to ER expression which peaks during the follicular phase (53). Furthermore, the *in vitro* treatment of breast cancer cells with estrogen and progesterone results in the switching from hormone-driven to growth factor-driven cell growth (54). Together, this suggests that the increasing concentrations of progesterone during the luteal phase may increase growth factor-dependent cancer cell function, and contribute to a poorer prognosis, as opposed to estrogen-dependent cancer cell function during the follicular phase. To date, only one study that examines the relationship between the timing of surgery and patient outcomes has assessed HER2 expression (Table IV). Liu *et al* (16) took into account HER2 expression, and found that HER2 expression did not fluctuate across the menstrual cycle, nor was it a prognostic factor for disease free survival. However, the authors did not consider the intensity of HER2 expression.

Several studies (11,14) have suggested that the effects of menstrual cycle phase are more pronounced in ER positive tumours, however the influence of PR and HER2 positivity on prognosis remains unclear. Expression of ER, PR and HER2 may be influenced by fluctuating concentrations of estrogen and progesterone, affecting cancer cell function and risk of metastasis. Changes in expression of hormone and growth factor

Table IV. ER, PR and HER2 expression.

Author	Number	Favourable outcome	Receptor expression								
			ER+	ER-	Ukn	PR+	PR-	Ukn	HER2+	HER2-	Ukn
Hrushesky *et al* (5)	44	Follicular	27[c]	17[c]	0	27[c]	17[c]	0	-	-	-
Senie *et al* (6)	283	Luteal	126	88	69	-	-	-	-	-	-
Badwe *et al* (7)	249	Luteal	145[c]	65[c]	39[c]	119[c]	84[c]	46[c]	-	-	-
Wobbes *et al* (17)	89	No relationship	52	26	11	59	23	7	-	-	-
Badwe *et al* (18)	271	No relationship	-	-	-	-	-	-	-	-	-
Corder *et al* (15)	157	Follicular	-	-	-	-	-	-	-	-	-
Veronesi *et al* (8)	1,175	Luteal	926[c]	249[c]	0[c]	905[e]	270[e]	0[e]	-	-	-
Saad *et al* (10)	84	Luteal	36[c]	48[c]	0[c]	48[c]	34[c]	2[c]	-	-	-
Saad *et al* (9)	96	Luteal	36[c]	68[c]	12[c]	48[c]	34[c]	14[c]	-	-	-
Minckwitz *et al* (11)	266	Luteal	120[d]	115[d]	31[d]	126[d]	96[d]	44[d]	-	-	-
Holli *et al* (19)	267	No relationship	126[c]	107[c]	34[c]	172[c]	61[c]	34[c]	-	-	-
Mohr *et al* (12)	289	Luteal	-	-	-	-	-	-	-	-	-
Vanek *et al* (27)	150	Perimenstrual	77	52	21	67	51	32	-	-	-
Milella *et al* (14)	248	Luteal	127 [a]	121[a]	0[a]	-	-	-	-	-	-
Nomura *et al* (23)	721	No relationship	400	284	37	-	-	-	-	-	-
Holmburg *et al* (24)	774	No relationship	-	-	-	-	-	-	-	-	-
Pujol *et al* (22)	360	No relationship	222[c]	138[c]	0[c]	264[c]	96[c]	0[c]	-	-	-
Takeda *et al* (26)	28	Perimenstrual	4	16	8	-	-	-	-	-	-
Thorpe *et al* (21)	412	No relationship	-	-	-	-	-	-	-	-	-
Grant *et al* (20)	834	No relationship	591	237	6	-	-	-	-	-	-
Kucuk *et al* (13)	90	Luteal	66[a]	24[a]	0[a]	-	-	-	-	-	-
Liu *et al* (16)	554	Follicular	341[b]	213[b]	0[b]	238	256	60	318[b]	168[b]	68[b]

[a]ER or PR status was not provided, however 'hormone receptor' expression was given; [b]The intensity of staining was measured; [c]receptor status was measured by the DCC method, using cut-off as <10 fmol/mg to define negative, and >10 fmol/mg to define positive; [d]measured by the DCC method using cut-off as <20 fmol/mg to define negative, and >20 fmol/mg to define positive; [e]measured by the DCC method using cut-off as <25 fmol/mg to define negative, and >25 fmol/mg to define positive. ER, Estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; -, receptor status not defined or measured; DCC, dextran-coated charcoal.

receptors may also affect clinical decision-making around use of adjuvant therapies in some premenopausal women (55,56), which could influence use of adjuvant treatments and explain why one stage of the menstrual cycle is associated with poorer survival outcomes. Therefore, hormone receptor and growth factor receptor expression may be a confounding factor on menstrual cycle phase-specific prognosis, or there may be alterations in tumour cell biology across the menstrual cycle that affect metastatic potential.

6. Biological mechanisms that link menstrual cycle phase to increased breast cancer cell dissemination

Several studies provide preclinical evidence that the manipulation of breast tumours during surgery or biopsy can increase the number of circulating tumour cells in the blood (57-60). The hormonal environment at the time of surgery may have effects on these circulating tumour cells and their microenvironment, to facilitate the establishment and survival of tumour cell metastases and contribute to phase-specific prognoses (61).

Estrogen and progesterone can modulate angiogenesis, vascular invasion, and the immune system, to promote a proangiogenic and immunosuppressive environment supportive of metastasis. In premenopausal women, breast tumours resected during the follicular phase of the menstrual cycle show increased incidence of vascular invasion (62). Preclinical studies have shown that expression of vascular endothelial growth factor (VEGF), a growth factor that plays key roles in angiogenesis and vascular invasion, is positively associated with estrogen concentration and its expression is blocked by estrogen antagonists *in vivo* (63,64). VEGF expression is highest during the follicular phase of the menstrual cycle, and expression is reduced with increasing concentrations of progesterone during the luteal phase (65). Any relationship between the timing of surgery and patient outcomes may be

Table V. Distribution of treatments within studies examining the relationship between menstrual cycle stage and prognosis.

Author	Number	Favourable outcome	Treatment					Adjusted for treatment
			Chemo-therapy	Hormonal therapy	Radiation	No therapy	Not defined in methods	
Hrushesky *et al* (5)	44	Follicular	31	-	28	13	-	No
Senie *et al* (6)	283	Luteal	-	-	-	-	283	No
Badwe *et al* (7)	249	Luteal	60	-	1	188	126 (N0 patients)	No[a]
Wobbes *et al* (17)	89	No relationship	46	-	-	-	43 (N0 patients)	No
Badwe *et al* (18)	271	No relationship	54	-	-	66	151 (N0 patients)	No
Corder *et al* (15)	157	Follicular	-	-	-	-	157	No
Veronesi *et al* (8)	1,175	Luteal	385	-	-	51	739 (N0 patients)	No
Saad *et al* (10)	84	Luteal	41	-	-	43	-	Yes[b]
Saad *et al* (9)	96	Luteal	43	-	-	53	50 (N0 patients)	No[a]
Minckwitz *et al* (11)	266	Luteal	151	-	-	115	-	No[a]
Holli *et al* (19)	267	No relationship	-	-	-	-	267	No
Mohr *et al* (12)	289	Luteal	35	-	-	99	149 (N0 patients)	No
Vanek *et al* (27)	150	Perimenstrual	-	-	-	-	150	No
Milella *et al* (14)	248	Luteal	248	-	-	-	-	No[a]
Nomura *et al* (23)	721	No relationship	582	429	-	-	-	No[a]
Holmburg *et al* (24)	774	No relationship	-	-	-	-	774	No
Pujol *et al* (22)	360	No relationship	-	-	-	-	360	No[a]
Takeda *et al* (26)	28	Perimenstrual	-	-	-	-	28	No
Thorpe *et al* (21)	412	No relationship	278	278	230	-	-	Yes
Grant *et al* (20)	834	No relationship	624	564	490	-	-	Yes[b]
Kucuk *et al* (13)	90	Luteal	60	-	-	30	-	Yes
Liu *et al* (16)	554	Follicular	-	-	-	-	554	No

Treatment information was unavailable in many studies. Many studies did not include information on hormonal therapies, or treatment regimens for node negative (N0) patients. Studies which included adjuvant therapy as a confounding variable, and adjusted for it in their outcomes are shown. -, the number of patients receiving this treatment was not defined in the methods of the paper. [a]adjuvant therapy was not adjusted for, however was noted that treatment distributions did not differ between groups; [b]studies adjusted for adjuvant therapy, however was not noted if this included adjusting for hormonal therapies in addition to chemotherapy.

influenced by increasing concentrations of estrogen during the follicular phase promoting a proangiogenic environment favourable for breast cancer metastasis.

Metastasis involves the migration of cells from the primary tumour in the breast to a distant site at which they must be able to establish. During the follicular phase, unopposed estrogen may facilitate metastasis by increasing the risk of dissemination of malignant cells during tumour handling during surgery. In addition to stimulating angiogenesis and vascular invasion, estrogen promotes the expression of genes involved in epithelial-to-mesenchymal transition (EMT), and allows for cells to detach and gain access to lymph and blood vessels (66). *In vitro* and *in vivo* stimulation with estrogen promotes proliferation of breast cancer cells and induces protease production. Simultaneously, estrogen downregulates E-cadherin expression, an effect which can be reversed with anti-estrogenic treatment, consequently increasing the invasive ability of tumour cells (67,68).

7. Biological mechanisms that link menstrual cycle phase to suboptimal immune response to breast cancer

The immune system plays a key role in removing cancer cells and preventing metastasis, and therefore an immunosuppressive environment at the time of surgery may increase the metastatic potential of cancer cells. Hormonal fluctuations during the menstrual cycle have direct and indirect effects on the immune system. Circulating estrogen during the follicular phase of the menstrual cycle can reduce immune activity, phagocytic activity, and alter expression of cytokines, which may promote tumour metastasis, establishment and survival. Conversely, progesterone can supress the effects of estrogen.

Macrophages and regulatory T cells (Tregs) play critical roles in the immune evasion abilities of breast cancer cells. The abundance of Tregs correlates with serum concentrations of estrogen; Tregs are most abundant during the

follicular phase of the menstrual cycle, and their abundance decreases during the luteal phase (69). Furthermore, treatment with estradiol promotes the proliferation of Tregs and enhances their immunosuppressive functions (70). Similarly, progesterone is known to have immunosuppressive activity, and regulates Treg abundance and phenotype (71). The abundance and function of macrophages also fluctuates across the ovarian cycle of mice, where lowest macrophage abundance is observed in the mouse mammary gland during the estrus phase, when concentrations of estrogen are highest (72,73).

Reduced natural killer (NK) cell abundance and activity is associated with increased metastatic incidence. Breast cancer patients with low NK activity are at a greater risk of developing metastatic recurrence (74). Furthermore, in mice, the metestrus phase of the estrous cycle shows lowest NK cell activity and interleukin-2 production, and is associated with the highest incidence of pulmonary metastasis (75). The effects of cycle phase on the abundance and activity of NK cells may be mediated by estrogen. Treatment of mice with estrogen results in inhibition of NK cell activity, and is associated with an increased incidence of pulmonary metastasis (76). Similarly, tamoxifen treatment of postmenopausal women resulted in enhanced NK cell activity (77). It is possible that high concentrations of estrogen during the follicular phase reduce NK activity, resulting in an immunosuppressive and pro-metastatic environment; conversely, high progesterone concentrations during the luteal phase promote an environment more resistant to tumour metastasis.

Estrogen also influences the expression of pro-inflammatory cytokines, including CSF1, CSF2, IFNG and TNFA. In mice, expression of pro-inflammatory cytokines is greatest at the estrus phase of the ovarian cycle, when concentrations of estrogen peak, and their increased expression is mitigated by progesterone during different ovarian cycle stages (78). Furthermore, estrogen treatment alone, or in combination with progesterone, can stimulate insulin-like growth factor 1 (IGF1) which can increase breast cancer cell proliferation and inhibit apoptosis (79,80). Conversely, concentrations of IGF1 in serum are reduced following progesterone treatment alone (79,81).

A relationship between the gut microbiome and the immune system has been described, where disturbance in diversity and alterations in relative abundance of different bacterial phyla and genera can influence the local and systemic immune environment (82) and increase breast cancer metastasis in mice (83). An association has been suggested between circulating concentrations of estrogen in blood and gut microbiota diversity, whereby increased circulating concentrations of estrogen contribute to a more diverse microbiome (84,85). If the stage of the menstrual cycle influences gut microbiota diversity, then cross-talk between the altered microbiome and the immune system may result in an environment that favours tumour cell metastasis, and thus the timing of surgery could influence survival outcomes. However, this phenomenon has not yet been explored.

Fluctuations in estrogen and progesterone across the menstrual cycle can influence immune cell abundance and activity, and change the cytokine environment. It is possible that altered immune function at a specific menstrual cycle phase may affect the metastatic ability of breast cancer cells; allowing for tumour cells to evade the immune system, and facilitate the spread, survival, and establishment of metastatic cells following surgery.

8. Conclusion

The current evidence from clinical studies and animal models supports the possibility that menstrual cycle phase at the time of surgery influences risk of tumour metastasis. However, given the conflicting results, it remains unclear whether there is an optimal time of the month to perform surgery. Currently, there is insufficient evidence to support a change in surgery scheduling for premenopausal breast cancer patients. This issue has dogged breast cancer surgery for decades; knowledge of an optimal time of the month to conduct surgery would be a simple, non-toxic, and cost-effective approach to improve patient outcomes. Key considerations for further studies are clear definitions for the different phases of the menstrual cycle based on both last menstrual period and circulating hormone concentrations, stratification by tumour subtype and nodal status, as well as consideration of confounding factors, including irregular menses, the use of oral contraceptives, and neoadjuvant and adjuvant therapy. The impact of tumour manipulation during both diagnosis and excision on patient prognosis should also be assessed. A significant problem with the current clinical studies is the lack of insight from mechanistic research that would elucidate the important variables to control for. While there are a number of plausible biological mechanisms that could collectively lead to altered survival (Fig. 1), supporting evidence is limited. Elucidation of the specific confounding factors, as well as biological mechanistic pathways that may explain the potential relationship between timing of surgery and survival will greatly assist in designing robust well-controlled clinical studies to evaluate this paradigm.

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Competing interests

The authors declare that they have no competing interests.

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