

# Menstrual Timing of Treatment for Breast Cancer

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**Although the hormone dependency of breast cancer has been recognized for nearly a century, the influence on disease progression of cyclical hormonal levels among premenopausal women has not been extensively researched. The findings of recent studies, assessing the effect on prognosis of the hormonal milieu at the time of surgery, have been conflicting. However, several reports have noted improved survival among patients with positive, axillary lymph nodes surgically treated in the later phase of the menstrual cycle when progesterone levels are elevated. Biologic support for the influence of menstrual timing is provided by cyclical patterns of cell division and cell death observed in normal breast tissue as well as potential tumor cell dissemination during surgery among patients with positive axillary nodes. Immune parameters, which also respond to cycling endogenous hormones, may influence the metastatic potential of circulating tumor cells. Comparisons among studies of menstrual timing of surgery have been complicated by differences in cycle divisions, extent of primary surgery, frequency of adjuvant therapy, duration of follow-up, and analytic procedures. Although several clinicians are now scheduling breast surgery of premenopausal women in relation to day of the menstrual cycle, a majority of surgeons have deferred consideration of menstrual timing until additional research is available. While waiting 5-10 years for the results of prospective studies, additional retrospective analyses, using carefully collected data, may provide clinical guidance. With increasing concern for issues related to women's health, multidisciplinary studies will be required to adequately characterize the influence of the menstrual cycle and other aspects of women's reproductive physiology on breast cancer and other medical conditions.** [Monogr Natl Cancer Inst 16:85-90, 1994]

Although Beatson (1) demonstrated the hormone dependency of breast cancer in 1896 by achieving remission of disease through bilateral oophorectomy, the influence of cyclical, endogenous hormonal levels on breast cancer prognosis among premenopausal women has not been extensively researched. Interest in the effect of the hormonal milieu at the time of breast cancer treatment was stimulated by the 1989 publication of Hrushesky et al. (2).

After observing a prognostic effect of the timing of mammary carcinoma excisions during the estrus cycle among laboratory animals (3), these investigators were encouraged to assess the

influence on survival of the hormonal milieu at time of breast cancer treatment of women (2). Among 41 patients, significantly better survival was observed when surgery had occurred between days 7 and 20 (midcycle) in contrast to surgery during the perimenstrual interval (2). An additional study of 40 breast cancer patients conducted by Spratt et al. (4) reported a similar survival benefit ( $P < .06$ ) in relation to these menstrual cycle intervals. However, several other investigators were unable to confirm these results (5-11). Rageth et al. (8) found no association between these cycle intervals and disease-free or overall survival among 271 patients. These authors, however, noted the frequency of positive nodes differed significantly by timing of surgery: 38% of patients treated in midcycle and 57% with perimenstrual timing of surgery. They suggested that cycling hormones may influence detectability of axillary lymph node metastases without influencing survival.

Other menstrual cycle divisions, based on hormone profiles, have been assessed by several researchers. Badwe et al. (12) contrasted days 3 through 12, an interval of unopposed estrogens, with days 0-2 and 13-32 when estrogen and progesterone levels were similarly stimulated. In this population of 249 patients, the proportion with recurrent disease was significantly greater (46%) when surgery had occurred between days 3 and 12, compared to 16% who relapsed following surgery at other times of the cycle ( $P < .001$ ). The impact of timing was confined to patients with positive axillary lymph nodes. In a second series of patients with shorter follow-up, these investigators again observed significant survival differences associated with timing of surgery (13). However, results of several other studies did not confirm these findings. Gnant et al. (14) found no difference in survival among 192 patients with positive nodes. Among 143 patients, survival differences in the opposite direction were found by Sainsburg et al. (15); surgery on days 3-12 was associated with improved prognosis ( $P = .03$ ), although multivariate analysis indicated timing was not an independent prognostic factor. Oral contraceptive use by more than 50% of these patients may have influenced results. Several other researchers with differing numbers of patients and less detailed

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analyses found no significant impact of this menstrual cycle division on prognosis (11,16-19).

The third cycle division was based on the hormone-dependent phases determined by setting the 14th day after onset of menses as the putative day of ovulation (20). The follicular phase, before ovulation, is characterized by a rise and fall of estrogen in the absence of progesterone; after ovulation, estrogen levels again increase accompanied by a rapid rise in progesterone. Survival in relation to surgery during the follicular or luteal phase was assessed in several reports with conflicting results (4,8,9,11). A statistically significant, increased risk of recurrence during 10 years of follow-up was observed by Senie et al. (9) only among positive node patients with tumor excision during the follicular phase compared with the luteal phase (hazard ratio = 2.1). In contrast, Rageth et al. (8) reported no difference in disease-free or overall survival among the 271 patients by the follicular or luteal phase, although analyses stratified by nodal status were not performed. Survival at 7 years among 30 patients treated during the follicular phase in the study by Spratt et al. (4) was 64% compared to 86% among 10 women whose surgery occurred during the luteal phase. Although life table analysis in this report was extended to 10 years, the proportion of patients censored after 7 years was too high for meaningful assessment. The only study in which endogenous hormone levels were used to categorize premenopausal patients was conducted by Ville et al. (21); four divisions of the menstrual cycle were created (perimenstrual, follicular, ovulatory, or luteal) based on blood levels of progesterone, estradiol, and luteotropin assessed the day before surgery. Although that report did not include Kaplan-Meier curves to show no differences in survival, their published table noted fewer recurrences among patients treated during the luteal phase (21).

A fourth cycle division was used by Saad et al. (22); primary surgery on days 1-12 was compared to surgery on days 13-36 among 96 patients (22). Surgery late in the cycle was associated with significantly greater disease-free survival (75%) in contrast

to surgery during the first 12 days (40%); the effect was greatest among patients with positive nodes ( $P < .01$ ).

## Comparisons Among Studies of Menstrual Cycle Timing

Table 1 presents several published reports with adequate data to assess survival following surgery early in the menstrual cycle (days 0-12, 3-12, and follicular phase) or later (luteal phase, days 0-2, and days 13-36). Four reports indicated significant differences in prognosis related to timing of surgery; a trend was noted in an additional study. Although multivariate analyses were conducted by some authors, analyses stratified by nodal status were not routinely performed. Several additional studies published as letters are not listed in Table 1 because of inadequate data for appropriate comparisons.

A meta-analysis combining data from 10 published reports (23) revealed a significant overall effect of the timing of surgery ( $P = .003$ ); however, the value of the summary statistic was diminished by the inclusion of studies with very different methodologies. The concordance among three similarly designed investigations, in which surgery early in the menstrual cycle had a significantly adverse effect on disease-free survival only among positive node patients, encourages continued assessment of the prognostic effect of the timing of surgery.

Comparisons among studies are hampered by differences in: divisions of the menstrual cycle, source and characteristics of study population, interval of patient accrual, primary and adjuvant treatment, stage of disease at diagnosis, duration and completeness of follow-up, and analytic methodology.

## Menstrual Cycle Divisions

The initial menstrual cycle division, based on animal research (3), was less appropriate than approximating the recognized menstrual cycle phases documented through extensive studies of female hormone profiles (20). Fig. 1 notes that three of the four

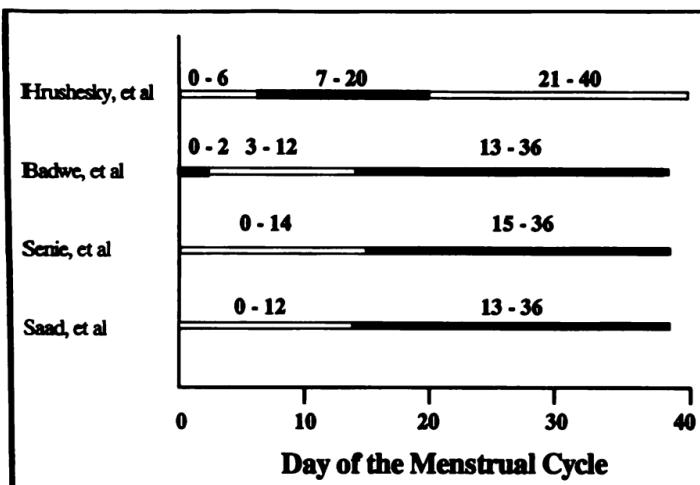
**Table 1.** Menstrual cycle timing of breast cancer surgery and survival\*

Author (ref. No.)	Years of accrual	% with LMP data	Sample size	Follow-up interval, y	Overall survival, %		Disease-free survival, %		Significance
					Follicular phase†	Luteal phase	Follicular phase†	Luteal phase	
Spratt et al. (4)	1972-1977	Not stated	40	7	64	86	Not stated	Not stated	Not stated
Rageth et al. (8)	1971-1988	71	217	5	82	80	55‡	46	Not significant
Senie et al. (9)	1976-1978	90	283	10	67	82	57	71	$P = .02$
Badwe et al. (12)	1975-1985	44	249	9	54	84	42‡	75‡	$P < .001$
Badwe et al. (13)	1985-1990	Not stated	150	Not stated	Not stated	Not stated	38‡	70‡	$P = .001$
Gnant et al. (14)	1977-1989	56	385	5	83	80	70	72	Not significant
Sainsbury et al. (15)	Not stated	42	143	10	70‡	48‡	Not stated	Not stated	$P = .06$
Nathan et al. (16)	1979-1988	58	132	Not stated	58‡	54‡	Not stated	Not stated	Not significant
Goldhirsch et al. (17)	Not stated	Not stated	225	10	65	55	54	44	Not significant
Powles et al. (18)									
RM		Not stated	205	11	60‡	62‡	Not stated	Not stated	Not significant
StG			108		65‡	74‡			
Low et al. (19)	1974-1986	30	125	Not stated	56‡	58‡	45‡	55‡	Not significant
Saad et al. (22)	1975-1988	30	86	10	39	74	40	75	$P = .01$

\*RM = Royal Marsden series; StG = St. George series; LMP = last menstrual cycle.

†Follicular phase: days 0-12, 3-12, 0-14.

‡Estimate from survival curve.



**Fig. 1.** Menstrual cycle divisions included in published studies of the prognostic effect of timing of surgery.

menstrual divisions greatly overlap, although they differ considerably from the initial scheme of Hrushesky et al. (3). Future studies must not rely on recalled dates of last menses and on usual cycle length. To avoid misclassification of menstrual phase, serum specimens should be obtained for assessment of the hormonal milieu at time of surgery (9,24,25).

## Patient Characteristics

Differing characteristics of the study subjects also complicate comparisons. Some studies included women from multiple institutions who were enrolled in adjuvant clinical trials (6,17), while others were case series from single or affiliated institutions (4,9-13). Exclusion of women reporting recent hormone use or pregnancy was not consistently noted. Stage of disease also differed considerably. In addition, sample sizes were frequently small and were restricted, primarily by lack of data on last menstrual period that limited the power to detect significant results (Table 1). Several reports included study patients with positive nodes and advanced disease, while others were confined to patients with earlier diagnosis. Because several studies observed survival differences only among positive node patients, subset analyses should be consistently performed.

## Primary and Adjuvant Treatment

Primary surgical treatment has evolved over the years of patient accrual among the timing studies. In the late 1970s, breast cancer surgery consisted of biopsy confirming the diagnosis followed by mastectomy and axillary dissection as a single surgical procedure; more recently, multiple surgical procedures are frequently performed. For consistency, several authors have studied the timing of *first* surgical intervention, regardless of the total number of procedures; the impact of the timing of multiple procedures on survival remains to be assessed. The frequency of adjuvant chemotherapy and radiation therapy also differs significantly among studies. Multivariate survival analyses using the Cox proportional hazards regression procedure provide a means for controlling differences in treatment; however, this statistical methodology was not uniformly applied.

## Duration and Completeness of Follow-up

The duration and completeness of follow-up also differed considerably among the publications. Although median follow-up intervals extended from 5 to 11 years, some study subjects were treated within 2 or 3 years of analysis. The low number of recurrences or deaths expected during limited follow-up intervals may have reduced the probability of detecting a true prognostic effect.

## Analytic Methodology

The quantity of data included in published timing studies varies greatly, hampering comparisons of study design and statistical methodology. However, several research groups with appropriately described methodology revealed similar results after applying multivariate analytic methods. The number of incompletely described published analyses increased concerns for chance detection of statistically significant findings that complicate all research endeavors. To address this issue, McGuire et al. (24) created a simulated study by randomly assigning a date of last menses to the patient histories included in their large database that emphasized the need for a prospective, carefully designed investigation.

## Menstrual Cycle Variability

Studies involving the menstrual cycle are complicated by the considerable variability women report in relation to age, reproductive history, medical conditions, psychosocial experiences, and other factors (26,27). However, extensive cohort studies have indicated that a majority of women experience regular cycles, averaging 28 days during most of their menstruating years (27). More research is required to adequately characterize the influence of cyclical hormonal patterns on women's health, especially the effect on hormone-dependent conditions.

## Influences of Menstrual Cycle on Breast Tissue

Studies of normal breast tissue have revealed changes in breast size, texture, and sensitivity during the menstrual cycle that have been frequently reported by women in relation to the cyclical hormonal milieu of the menstrual cycle. Among several factors studied are breast volume (28-30), histologic changes including cell division and cell death (31-33), thymidine-labeling index (34,35), estrogen and progesterone receptor levels (36-39), and immune parameters including natural killer (NK) cells (40,41).

Variations in breast volume and sensitivity during the menstrual cycle have been reported and measured by several researchers (28-30). Magnetic resonance imaging (MRI) documented marked increases in total breast and parenchymal volumes as well as water content in the latter phase of the cycle following ovulation (30). These findings correspond to those reported by others, using more conventional measurement techniques (28,29). Drife (28) suggested the cyclical changes in the breast may be linked to malignant transformation.

Using thymidine-labeling index techniques, several investigators have documented the biorhythm of cell division and cell

deletion in the breast tissue of normal women, corresponding to the shifting hormonal milieu of the menstrual cycle; rates of mitosis and apoptosis decreased with age at time of breast biopsy and were altered by exposure to exogenous hormones (31,32). Others (33-35) have observed menstrual cycle-dependent histologic patterns in epithelium and stroma of normal breast tissue.

Conflicting results have been reported when estrogen and progesterone receptors were studied in relation to phase of the menstrual cycle at time of tumor excision. Several reports found no significant association of receptor levels with menstrual cycle phase at the time of tumor excision (36,38,39), while others found increasing mean concentrations during the luteal phase (37). These conflicting findings may reflect differences in hormonal patterns associated with age at diagnosis.

Lowered immune parameters observed during the follicular phase associated with rising levels of unopposed estrogens may potentiate metastatic spread at the time of tumor excision. Some investigators have reported that NK cell activity falls significantly before ovulation among premenopausal breast cancer patients and healthy women (40,41). Interleukin 1 secretion from cultured monocytes was found to increase with luteal phase concentrations of progesterone (42), and a significant decrease in phagocytic activity of mononuclear cells early in the menstrual cycle was reported by Stratton et al. (43). Mice treated with  $\beta$ -estradiol exhibited lower NK cell activity and enhanced susceptibility to metastases (44). Thus, the diminished NK levels associated with the follicular phase may be further compromised following surgery early in the menstrual cycle, resulting in reduced host resistance to seeding of metastases by circulating tumor cells.

## Influences of Menstrual Cycle on Mammary Tumor Cells

Ervin, Wicha, et al. (45,46) noted that mammostatin, a protein produced by normal human mammary cells, controls cell proliferation. Decreased production of mammostatin by transformed compared with normal mammary cells may contribute to the loss of growth control associated with malignancy. Mammostatin levels were found to correspond to the hormonal milieu of the menstrual cycle (46).

In vitro studies revealed an increase in the growth fraction (GF) of human breast adenocarcinomas in the presence of estrogen; however, when both estrogen and progesterone were present, GF was significantly depressed regardless of receptor status (47). Other investigations of human breast cancer cells noted the antiproliferative activity of progesterone, independent of estrogen, suggesting progestin therapy may retard tumor growth (48,49). These studies support the hypothesis that elevated estrogen levels unopposed by progesterone at the time of surgery during the follicular phase may enhance the growth of circulating cancer cells in patients with positive axillary nodes who have a higher probability of metastatic seeding. McGuire (50) suggested a short course of tamoxifen might be administered before surgery, if additional research convincingly demonstrates the effect of timing. Some clinicians have proposed progesterone administration at the time of surgery to

simulate the luteal phase may enhance prognosis (Holland J: personal communication).

## Potential Biologic Mechanisms

Endogenous hormones may influence the growth and metastatic potential of tumor cells released into the bloodstream during surgery (51). Concern for the risk of surgery-induced tumor cell dissemination led to the initiation of one of the earliest adjuvant chemotherapy protocols in which a short course of thioguanine was administered perioperatively (52). Treated patients had a significant survival advantage compared with controls during 10 years of follow-up; however, the effect was limited to premenopausal patients with positive axillary nodes (52). In a large Scandinavian study (53), 20 years after breast cancer diagnosis, a short course of chemotherapy immediately after surgery was associated with a significantly reduced risk of recurrence, especially among node-positive patients. Although some studies have found short-term chemotherapy inadequate and favor initiation of systemic therapy several weeks after surgery (54), renewed interest in perioperative treatment has been expressed (55). One potential mechanism of action on menstrual timing for breast surgery may be the influences of the hormonal milieu on perioperative seeding of metastases.

Some gynecologists have hypothesized that surgery during the follicular phase may delay ovulation, lengthening the interval during which the growth of circulating cancer cells may be enhanced by unopposed estrogens. This theory is supported by Soules et al. (56), who observed reduced progesterone levels during the luteal phase in patients following surgery under general anesthesia. They suggested that ovarian steroid production was temporarily compromised by the toxic effect of general anesthesia (56). Further studies are needed to assess the influence that general anesthesia has on menstrual cycle patterns. An additional hormonal influence of surgery was reported by Barni et al. (57), who found postoperative prolactin levels varied with the phase of the menstrual cycle at time of surgery; high prolactin levels have been associated with poor prognosis.

Therefore, several potential biologic mechanisms associated with breast cancer prognosis may be related to the timing of tumor excision and possibly subsequent surgery, especially in those with positive node axillary lymph nodes. Further research must include biochemical assessment of menstrual phase at the time of surgery and determination of the interval between last preoperative and first postoperative menses to appropriately categorize study subjects.

## Future Research

Several investigators have called for prospective studies to address many of the issues uncontrolled in the retrospective comparisons, using data collected for unrelated analyses (2,9,24). Retrospective analyses may be biased because of the inconsistency of menstrual cycle information recorded in medical charts among several studies listed previously. Although a randomized clinical trial has become the standard, the complexity of scheduling randomly allocated patients, with unconfirmed stage of disease, could jeopardize the investigation.

Ethical issues must also be considered, and informed consent may be difficult to obtain (58). Several prospective, observational studies are under way, which may clarify some of the relationships between the hormonal milieu at time of surgery and disease progression, including a multicenter study (59) in England and an institution-based study (Zhida S: personal communication) in Canada.

Although several clinicians are now scheduling breast surgery on premenopausal women in relation to day of the menstrual cycle, a majority of surgeons have deferred consideration of menstrual timing until additional research is available. Prospective studies may be optimal to clarify the suggested relationships; however, additional retrospective analyses, using carefully collected data, may provide clinical guidance while waiting for results during the 5-10 years of follow-up.

## Menstrual Timing of Other Aspects of Breast Cancer Care

Concern with timing during the menstrual cycle may influence other aspects of breast cancer care, including the scheduling of screening and chemotherapy. In recognition of changes in breast tissue corresponding to the estrogen-progesterone sequence of the menstrual cycle, some gynecologists advise breast examinations during the follicular phase when breast tissue is softest (60). Similarly, premenopausal women enrolled in the Canadian National Breast Screening Study were advised to schedule their appointments the week after onset of menses (Baines C: personal communication). Consensus on this recommendation was not evident in a limited survey of mammographic centers in New York City. Only one private facility specifically stated that a mammogram would be easier to read and the procedure more comfortable if performed shortly after menses; no specific interval was indicated by the other centers contacted.

Menstrual timing of systemic therapy received little interest until a recent report by Whitaker et al. (61). These investigators observed reduced fertility when cytotoxic chemotherapy was administered to laboratory animals at a time of rapid follicular cell division during the estrus cycle. An additional question may be related to the potential effect of menstrual timing of systemic therapy on drug tolerance and immediate side effects.

As interest and concern for women's health increase, multidisciplinary studies should be conducted to adequately characterize the influence of the menstrual cycle and other aspects of women's reproductive physiology on health and disease, including breast cancer.

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## Note

Presented in part at the Breast Cancer in Younger Women Conference, National Institutes of Health, Bethesda, Md., January 28, 1993.