

## Mastectomy and Oophorectomy by Menstrual Cycle Phase in Women With Operable Breast Cancer

Richard R. Love, Nguyen Ba Duc, Nguyen Van Dinh, Tian-Zhen Shen, Thomas C. Havighurst, D. Craig Allred, David L. DeMets

**Background:** It is unclear whether the phase of the menstrual cycle in which primary surgical treatment occurs influences disease-free survival (DFS) and overall survival (OS) in premenopausal women with breast cancer. We investigated this question in the context of a clinical trial comparing mastectomy alone with mastectomy plus adjuvant oophorectomy and tamoxifen in premenopausal women with operable breast cancer. **Methods:** The date of the first day of the last menstrual period (LMP) was used to estimate the phase of the menstrual cycle when the surgeries were done. Follicular phase was defined as day 1–14 from LMP. Luteal phase was defined as day 15–42 from LMP. DFS and OS statistics were determined and analyzed by Cox proportional hazards ratios and Kaplan–Meier methods. All statistical tests were two-sided. **Results:** We analyzed results for 565 women who reported an LMP within 42 days before surgery. For women in the mastectomy only arm ( $n = 289$ ), there were no differences in DFS or OS by menstrual cycle phase. For women in the adjuvant treatment arm ( $n = 276$ ), those whose surgery occurred during the luteal phase ( $n = 158$ ) had better DFS (relative risk [RR] = 0.54; 95% confidence interval [CI] = 0.32 to 0.96;  $P = .02$ ) and OS (RR = 0.53; 95% CI = 0.30 to 0.95;  $P = .03$ ) than those whose surgery occurred during the follicular phase ( $n = 118$ ). Moreover, women whose surgery occurred during the luteal phase and who received adjuvant therapy had better 5-year DFS than did women whose surgery occurred during the follicular phase (84%; 95% CI = 78% to 90% versus 67%; 95% CI = 58% to 78%;  $P = .02$ ); they also had better OS (85%; 95% CI = 78% to 92% versus 75%; 95% CI = 66% to 84%;  $P = .03$ ). **Conclusions:** The phase of the menstrual cycle at which surgery was done had no impact on survival for women who received mastectomy only. However, women who received a mastectomy and surgical oophorectomy and tamoxifen during the luteal phase had better outcomes than women who received surgery during the follicular phase. [J Natl Cancer Inst 2002;94:662–9]

Over a century ago, Beatson (1) reported on the positive impact of oophorectomy in premenopausal women with metastatic breast cancer. However, only in more recent years has this observation led to a detailed evaluation of this intervention early in the natural history of breast cancer. In 1992, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (2) suggested that, contrary to general opinion at the time, adjuvant oophorectomy by surgery or radiation resulted in a sustained favorable impact on disease-free survival (DFS) and overall survival (OS). This finding encouraged several clinical trials (3–7),

particularly of medical oophorectomy with luteinizing hormone-releasing hormone (LHRH) agonists, whose results have suggested that in hormone-receptor-positive, tumor-bearing patients, ablation of ovarian function does indeed provide survival benefit. Moreover, a laboratory report by Ratajczak et al. (8) and a clinical patient report by Hrushesky et al. (9) suggested that the timing of breast cancer surgery during the menstrual cycle could influence long-term outcomes. When the beneficial effects of surgery at specified times in the menstrual cycle could not be reproduced (10–12) using the periovulatory/perimenstrual divisions proposed by Hrushesky (9), Badwe et al. (13) presented a refined hypothesis emphasizing the adverse effects of unopposed estrogen during the follicular phase of the menstrual cycle. Although a large study by Veronesi et al. (14) supported the Badwe hypothesis (13), a similar size study by Kroman et al. (15) did not. A review of Badwe's hypothesis (13) and a meta-analysis of many of the reported studies (16), all retrospective, suggest that further research is needed to address the confounding influences and to investigate possible mechanisms for such postulated beneficial effects. Some of the potential confounding factors are immune function (17), growth factors (18), and the hormonal effects of surgery (19–21), all of which have been suggested to co-vary with phase of the menstrual cycle. These effects might lead to greater adverse impact of tumor dissemination suggested to occur at the time of breast cancer surgery (22).

In this historical context, we began a prospective randomized controlled trial of surgical oophorectomy and tamoxifen adjuvant therapy in Vietnamese and Chinese premenopausal women in 1993. The first results of the study show a highly statistically significant benefit in DFS and a nominally statistically significant benefit in OS from the adjuvant treatment (23). In our trial, we recorded the date of the last menstrual period (LMP) before oophorectomy surgery, which in the majority of our study patients was done under the same anesthesia as mastectomy. Patients were diagnosed with breast cancer by aspiration cytology alone and, thus, mastectomy was the only breast surgical pro-

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cedure they underwent. We report here the results of an exploratory evaluation of the impact of oophorectomy performed during the follicular or luteal phase of the menstrual cycle, as defined by Badwe et al. (13,16), on the DFS and OS of patients in this randomized clinical trial.

## SUBJECTS AND METHODS

### Subjects and Study Design

The main initial results, study design, treatments, quality control, definitions, estrogen and progesterone receptor protein evaluation methods, and the histologic subtyping and grading for the trial, from which a subset of patients is reported upon here, have been published (23). Briefly, from April 7, 1993, through June 30, 1999, 662 Vietnamese and 47 Chinese premenopausal women (defined as those with at least one menstrual period in the last 12 months) with operable breast cancer [Tumor–Node–Metastasis stages II through IIIA (24)] were recruited into a randomized clinical trial of mastectomy with adjuvant surgical oophorectomy and tamoxifen (20 mg by mouth per day) for 5 years versus mastectomy alone. In the mastectomy-alone group, subsequent oophorectomy and tamoxifen treatment were recommended for those who developed metastatic cancer.

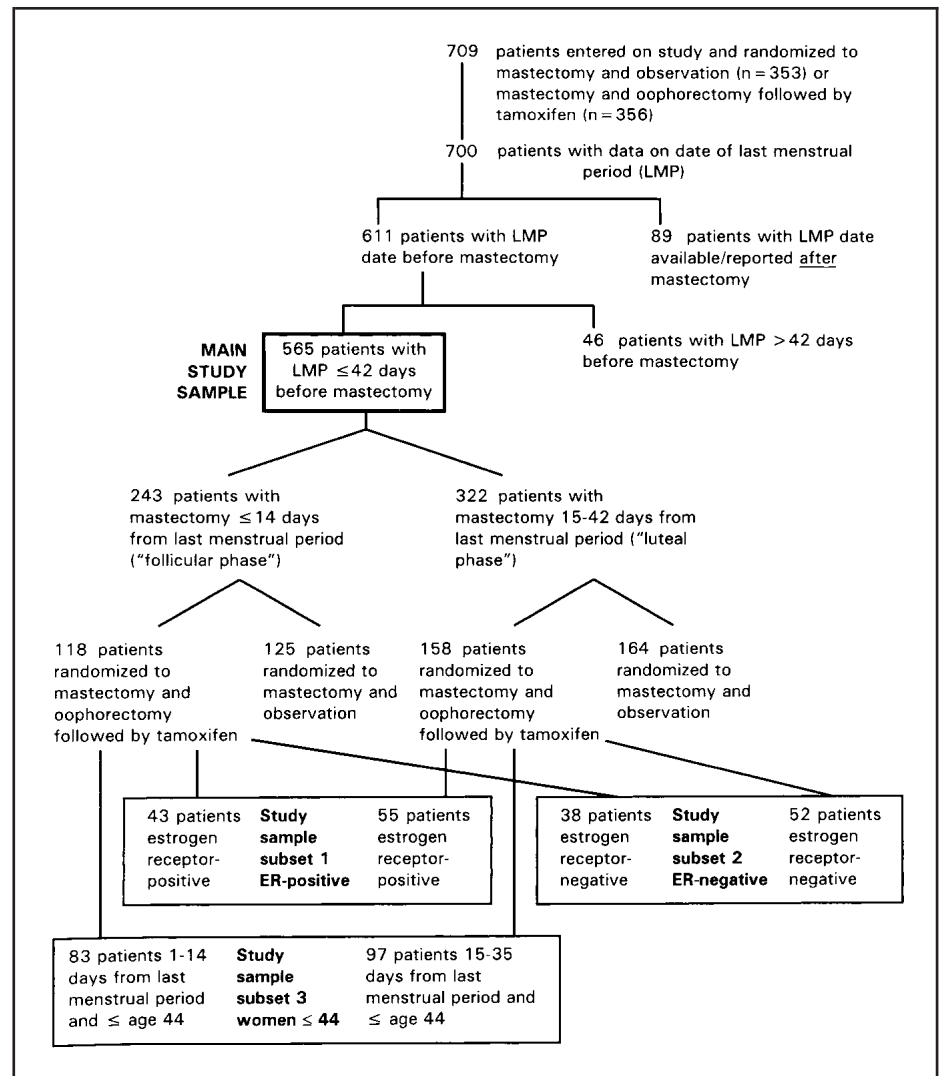
All estrogen receptor (ER) studies were done 2–7 years after

surgery on paraffin-embedded tissues available for two thirds of study patients (23). Each participant gave written informed consent. The study was reviewed and approved by an institutional review board at the University of Wisconsin, by the Office for Protection of Research Risk of the U.S. National Institutes of Health, by the Scientific and Technical Council of the Ministry of Health of Vietnam, and by institutional review committees in China. A data monitoring committee of five experts from North America periodically reviewed the overall trial conduct and the primary, secondary, and safety results.

### Statistical Methods

The results reported here are from exploratory *post hoc* analyses of subsets of trial participants as defined in Fig. 1. The chi-square ( $\chi^2$ ) test and the Wilcoxon test were used to analyze differences in categorical and ordinal baseline variables, respectively (25). Univariate and multivariate analyses for DFS and OS used a log-rank test and the Cox proportional hazards model (26,27). The model did not differ substantially from proportional hazards. DFS and OS curves were calculated using Kaplan–Meier methods (28). All computations were performed with SAS software (version 6.12; SAS Institute, Cary, NC). All *P* values were calculated with two-sided tests of significance.

**Fig. 1.** Consort trial flow diagram of patients with operable breast cancer who were randomly assigned to receive mastectomy and observation or mastectomy and oophorectomy and tamoxifen.



## RESULTS

### Study Samples

In this study, patients were randomly assigned to receive adjuvant therapy with oophorectomy and tamoxifen or observation after primary surgical treatment with mastectomy (Fig. 1). Of the 709 patients who enrolled in the study, 89 patients were excluded from the primary analyses reported here because they entered the study after having undergone a mastectomy within the previous 2 months, they were without data on individual cycle length, or the estimates of the date of their last menstrual period were considered unreliable. Of the remaining 611 patients, 46 (7.5%) reported a first day of their last menstrual period more than 42 days before mastectomy with or without oophorectomy (Fig. 1), and 97 (15.9%) reported a last menstrual period more than 28 but less than 43 days from the date of the surgeries. These data are consistent with those showing that 12% and 31% of subjects were older than 48 years and older than 45 years, respectively, when they entered the study and thus were at risk for perimenopausal anovulatory cycles. We assumed that a majority of the 46 patients with more than 42 days since their last menstrual period were anovulatory and, therefore, we excluded them from the primary analyses.

The main study sample had 565 patients who reported a last menstrual period 42 or fewer days before surgery (Fig. 1). For further analyses, the patients who were randomly assigned to receive oophorectomy and tamoxifen were segregated into three study subsets. Subset 1 contained 98 patients who, on the basis of available ER data, were ER-positive. Subset 2 contained 90 patients who, on the basis of available ER data, were ER-negative (Fig. 1). Subset 3 contained 180 patients who were younger than 45 years and who reported a last menstrual period less than 36 days before the surgeries (Fig. 1). For subset 3, we assumed that these criteria would lead to the inclusion of very few anovulatory women (in contrast with the situation for the main study samples, in which modest percentages of anovulatory women were likely to be included). The median follow-up time was 3.6 years (range = 10 days through 8 years, 3 months),

with the status unknown for longer than 6 months for fewer than 5% of the patients.

There was no statistically significant difference between the 565 patients with a reported last menstrual period at 42 or fewer days before the surgery and the 144 patients who entered the study but who were not included in the analyses regarding age, weight, pathologic tumor size, percentage of patients with pathologically positive axillary nodes, numbers of positive axillary nodes, or percentage of patients with histologic grade III tumors. For the prognostic factors listed in Table 1, the population of patients with hormone receptor data did not statistically significantly differ from the population without these data.

Table 1 shows that in the two intervention groups, in those who received oophorectomy and tamoxifen, a difference in weight was the only statistically significant variable between those who had surgery in the follicular phase and those who had surgery in the luteal phase of the menstrual cycle. For patients 44 years old and younger (subset 3, Fig. 1), there were no differences in the major prognostic factors between those patients whose surgery was performed during the follicular phase (1–14 days) and those whose surgery was performed during the luteal phase (15–35 days) of the menstrual cycle.

### Principal Findings

To determine whether surgery during a particular menstrual cycle phase was associated with differences in the DFS or OS of the main study samples, we performed univariate proportional hazard analyses. Table 2 shows that the DFS and OS were similar for patients in the observation arm regardless of phase of the menstrual cycle. Compared with patients in the observation arm, patients treated with oophorectomy and tamoxifen benefited from this adjuvant treatment; however, the magnitude of the benefit for DFS was statistically significant only for those treated during the luteal phase of the menstrual cycle (RR [risk ratio] = 0.45; 95% CI = 0.28 to 0.73;  $P = .001$ ). Compared with patients treated with oophorectomy and tamoxifen during the follicular phase of the menstrual cycle, those in the same arm treated during the luteal phase of the menstrual cycle had a

**Table 1.** Demographic and prognostic characteristics of Vietnamese and Chinese women with operable breast cancer randomly assigned to receive adjuvant oophorectomy and tamoxifen versus observation after mastectomy (main study samples)\*

	Adjuvant oophorectomy and tamoxifen patients			Observed patients		
	Follicular phase (n = 118)	Luteal phase (n = 158)	<i>P</i> value for difference†	Follicular phase (n = 125)	Luteal phase (n = 164)	<i>P</i> value for difference†
Mean age, y	41.3	41.7	.53	40.5	41.5	.14
Age >45 years, %	29.7	33.8	.47	27.2	32.3	.35
Age >48 years, %	13.6	9.6	.30	9.6	14.6	.20
Mean weight, kg	47.6	49.1	.05	48.2	48.2	.67
Pathologic tumor size, cm	3.3	3.1	.18	3.4	3.3	.92
Pathologically axillary node-positive, %	52.6	53.6	.88	52.5	50.9	.80
Mean number of positive axillary nodes	4.8	4.0	.44	4.4	4.0	.67
Histologic grade III tumors, %	13.5	11.1	.61	11.5	9.2	.59
<i>For subsets with data‡</i>						
Estrogen receptor-positive, %	53.1	51.4	.82	69.5	66.7	.67
Progesterone receptor-positive, %	65.4	59.4	.40	67.5	63.0	.52

\*Determination of the phase of the menstrual cycle was made on the basis of the date of the last menstrual period before surgery. Follicular phase patients were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients were defined as those reporting a last menstrual period 15–42 days from the time of surgery.

†For age, weight, pathologic tumor size, and number of positive axillary lymph nodes, a Wilcoxon test was used; for the other four characteristics, a chi-square ( $\chi^2$ ) test was applied. All *P* values were two-sided.

‡For approximately two thirds of patients in each of the four groups in the table, hormone receptor data was available.

**Table 2.** Proportional hazards models for disease-free survival (DFS) and overall survival (OS) for interaction of mastectomy with or without concurrent oophorectomy and menstrual phase status at surgery\*

Intervention	Menstrual cycle phase†	n	DFS		OS	
			RR (95% CI)	P	RR (95% CI)	P
<i>Main study samples‡</i>						
Observation	Follicular	125	1		1	
Observation	Luteal	164	0.94 (0.63 to 1.41)	.77	0.83 (0.51 to 1.34)	.44
Observation	Follicular	125	1		1	
Oophorectomy/tamoxifen	Follicular	118	0.78 (0.50 to 1.20)	.29	0.88 (0.53 to 1.46)	.63
Observation	Luteal	164	1		1	
Oophorectomy/tamoxifen	Luteal	158	0.45 (0.28 to 0.73)	.001	0.58 (0.33 to 1.01)	.06
Oophorectomy/tamoxifen	Follicular	118	1			
Oophorectomy/tamoxifen	Luteal	158	0.54 (0.32 to 0.96)	.02	0.53 (0.30 to 0.95)	.03
<i>Subset 1: estrogen receptor-positive§</i>						
Oophorectomy/tamoxifen	Follicular	43	1			
Oophorectomy/tamoxifen	Luteal	55	0.32 (0.10 to 1.01)	.05	0.51 (0.12 to 2.16)	.36
<i>Subset 2: estrogen receptor-negative§</i>						
Oophorectomy/tamoxifen	Follicular	38	1			
Oophorectomy/tamoxifen	Luteal	52	0.53 (0.26 to 1.11)	.09	0.39 (0.18 to 0.86)	.02
<i>Subset 3: age ≤44 years§</i>						
Oophorectomy/tamoxifen	Follicular	83	1			
Oophorectomy/tamoxifen	Luteal	97	0.36 (0.20 to 0.65)	.008	0.37 (0.19 to 0.72)	.003

\*Univariate analyses. Risk ratio (RR) of 1 refers to the referent; CI = confidence interval.

†Determination of the phase of the menstrual cycle was made on the basis of the date of the last menstrual period before surgery. Follicular phase patients were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients were defined as those reporting a last menstrual period 15–42 days from the time of surgery.

‡Main study samples refers to all patients who provided a date of their last menstrual period that occurred within 43 days of the surgery (n = 565).

§Of the 276 patients who were randomly assigned to receive adjuvant oophorectomy and tamoxifen, 98 were included in subset 1 (estrogen receptor-positive cancers), 90 were included in subset 2 (estrogen receptor-negative tumors), and 180 were included in subset 3 (age ≤44 years).

statistically significant benefit for DFS (RR = 0.54; 95% CI = 0.32 to 0.96;  $P = .02$ ) and for OS (RR = 0.53; 95% CI = 0.30 to 0.95;  $P = .03$ ) (Table 2).

In multivariable analyses that used data from the main study samples, there was no association between menstrual cycle phase and DFS or OS for patients in the observation arm. However, for patients in the oophorectomy and tamoxifen arm, those who had surgery during the luteal phase of the menstrual cycle had RRs for DFS and OS of 0.38 (95% CI = 0.18 to 0.79;  $P = .01$ ) and 0.41 (95% CI = 0.19 to 0.88;  $P = .02$ ) compared with those who had surgery during the follicular phase of the menstrual cycle in models that included the square root of the number of positive axillary lymph nodes (this variable provides a better fit to the data than other single variables or combinations of variables used to describe axillary nodal status), pathologic tumor size, histologic tumor grade III, and ER-positive and progesterone receptor-positive status. In these models the directions and the magnitudes of the risk associated with each of the prognostic variables were as expected. Analysis for any interaction of the phase of surgery with these prognostic variables showed no statistically significant associations; for an interaction of menstrual phase at surgery with ER status,  $P = .12$ .

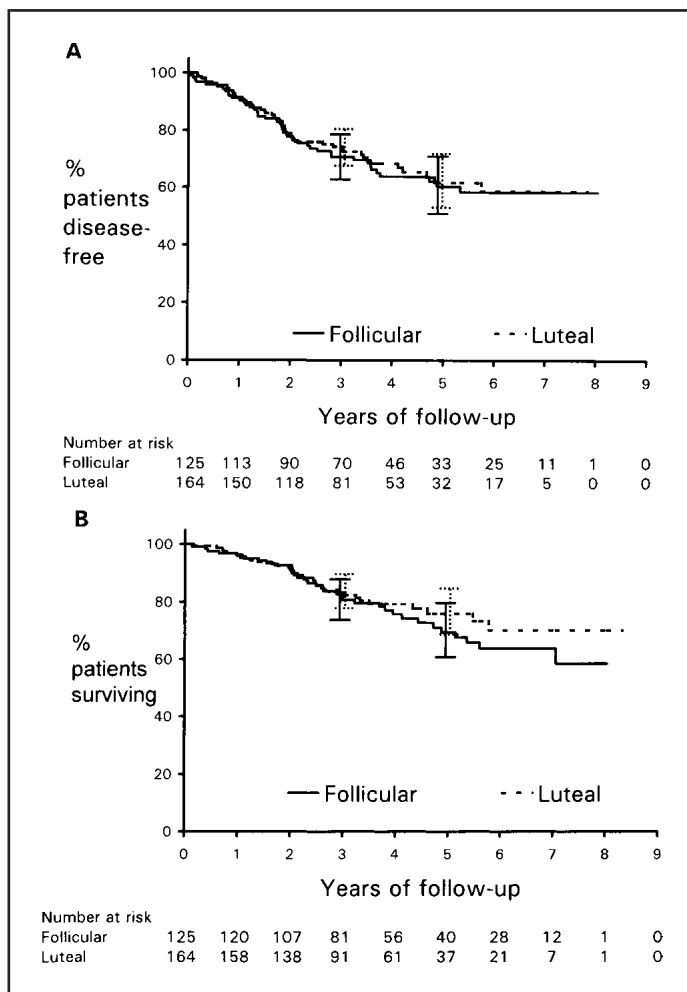
To further investigate the association of menstrual cycle phase and response to adjuvant oophorectomy, we performed Kaplan–Meier analysis of the DFS and OS for the main study sample. As shown in Fig. 2, among patients in the mastectomy only arm there was no statistically significant difference in DFS and OS for those who had surgery during the follicular phase of the menstrual cycle versus those who had surgery during the

luteal phase. There was a statistically significant benefit in DFS for patients in the oophorectomy and tamoxifen arm who had surgery during the luteal phase compared with patients in the observation arm who had surgery during the luteal phase ( $P = .001$ ) and a benefit for oophorectomy/tamoxifen patients who had surgery during the follicular phase compared with follicular phase observation arm patients ( $P = .016$  for DFS) (data not shown). Kaplan–Meier estimates showed that patients in the oophorectomy and tamoxifen arm who had surgery during the luteal phase of the menstrual cycle had a statistically significant benefit compared with patients who had surgery during the follicular phase ( $P = .02$  for DFS and  $P = .03$  for OS) (Fig. 3).

### Exploratory Findings

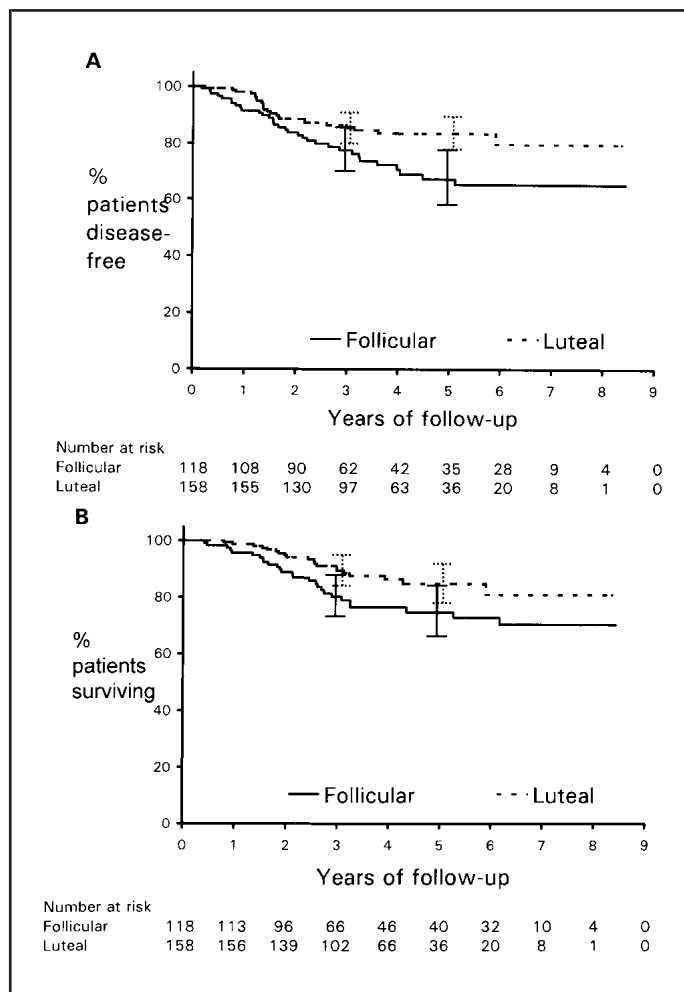
In subset 1, patients with ER-positive cancers in the oophorectomy and tamoxifen arm who had surgery during the luteal phase of the menstrual cycle had better DFS than those who had surgery during the follicular phase ( $P = .04$ ) (Fig. 4 and Table 2). In subset 2, patients with ER-negative cancers in the oophorectomy and tamoxifen arm who had surgery during the luteal phase of the menstrual cycle had better DFS ( $P = .04$ ) and OS ( $P = .02$ ) than did those who had surgery during the follicular phase (Fig. 4 and Table 2).

When univariable or multivariable proportional hazards and Kaplan–Meier analyses were conducted in which women with a last menstrual period ≤10, ≤12, or ≤16 days, or 3–14 days before the combined mastectomy and oophorectomy surgery were defined as those in the follicular phase, only minor differences in the results were found relative to those presented above.



**Fig. 2.** Kaplan-Meier curves for disease-free survival (A) and overall survival (B) patients with operable breast cancer who were randomly assigned to the mastectomy and observation arm. Follicular phase patients ( $n = 125$ ) (solid line) were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients ( $n = 164$ ) (dotted line) were defined as those reporting a last menstrual period 15–42 days from the time of surgery. Vertical error bars represent the 95% confidence intervals for the number of patients at risk at 3 and 5 years. There was no statistically significant difference between the curves as determined by the log-rank test.

Similarly, if women aged 44 years or younger who reported a menstrual period 35 days or fewer before the surgery were defined as being in the luteal phase, there was no difference in DFS and OS determined by Kaplan-Meier analyses between patients in the observation arm, regardless of menstrual cycle phase ( $P = .54$  and  $P = .96$ , respectively) (Fig. 5), whereas for those patients in the oophorectomy and tamoxifen arm (subset 3), DFS and OS were better for women treated during the luteal phase than for those treated during the follicular phase ( $P = .001$  and  $P = .005$ , respectively) (Fig. 6 and Table 2). The apparently greater differences in DFS and OS between the follicular and luteal phases of the treated study subset sample (Fig. 6) compared with the study main sample (Fig. 3) appear mainly consequent to a worse prognosis for follicular phase patients in the study subset sample. Analyses that include the 46 patients with a last menstrual period more than 42 days before mastectomy result in findings very similar in all respects to those for the main samples.

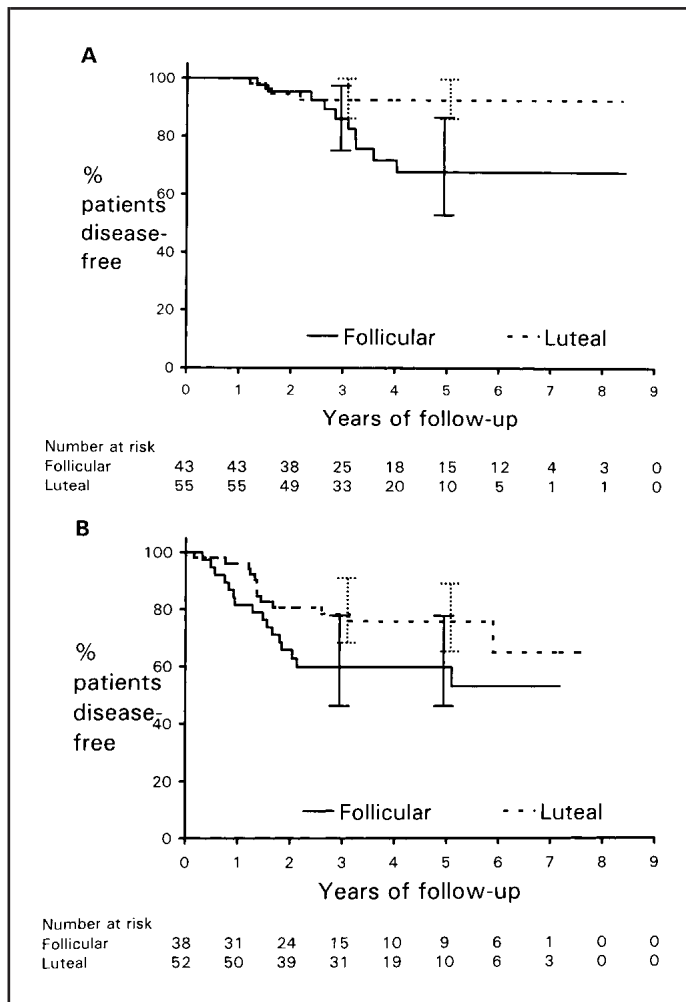


**Fig. 3.** Kaplan-Meier curves for disease-free survival (DFS) (A) and overall survival (OS) (B) patients with operable breast cancer who were randomly assigned to mastectomy and oophorectomy on the same day, followed by tamoxifen therapy daily begun within 7 days. Follicular phase patients ( $n = 118$ ) (solid line) were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients ( $n = 158$ ) (dotted line) were defined as those reporting a last menstrual period 15–42 days from the time of surgery. Vertical error bars represent the 95% confidence intervals for the number of patients at risk at approximately 3 and 5 years. There was a statistically significant difference in the curves for DFS ( $P = .02$ ) and OS ( $P = .03$ ).

## DISCUSSION

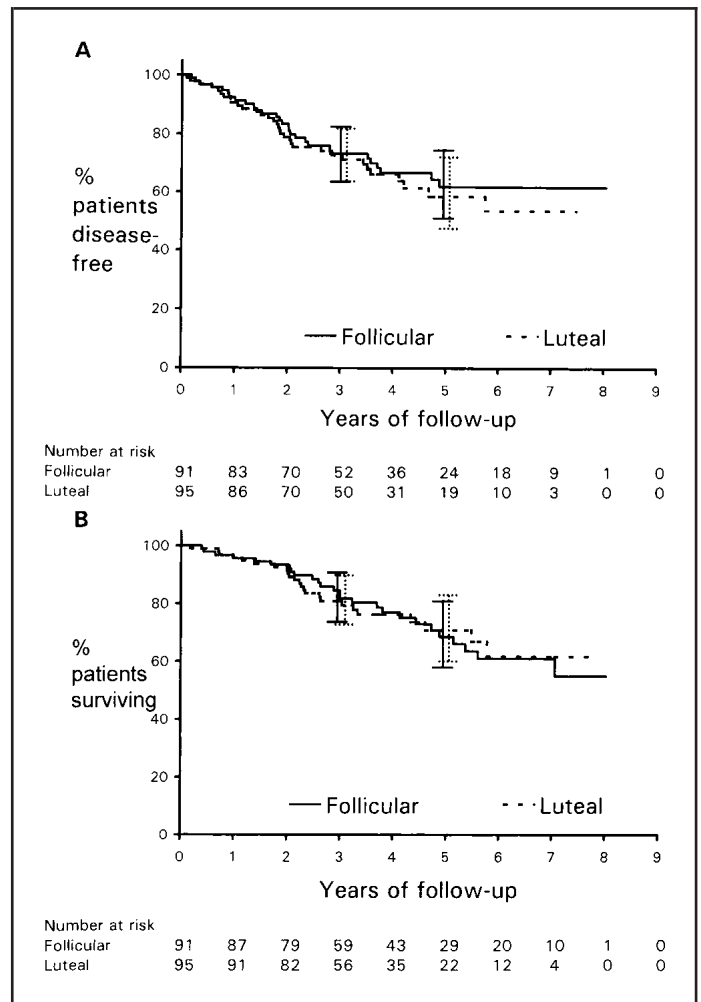
The relationship of menstrual cycle phase at the time of primary treatments for breast cancer to DFS and OS in premenopausal women is uncertain (16). In this study we investigated this relationship in two populations: one receiving mastectomy treatment alone, in which we found no association of outcomes with menstrual cycle phase, and one receiving mastectomy and simultaneous oophorectomy, in which we found a statistically significant association with luteal phase surgeries and greater DFS and OS benefit.

In this study, using definitions of follicular and luteal phase derived from the reported date of the last menstrual period as surrogates to classify women with different hormonal conditions at the time of mastectomy and oophorectomy surgeries is clearly imperfect. Badwe et al. (29) found that, without blood hormone studies, at least 16% of premenopausal women are misclassified on the basis of reported menstrual cycle history. In our study,



**Fig. 4.** Kaplan-Meier curves for disease-free survival (DFS) in patients with estrogen receptor (ER)-positive (A) or ER-negative (B) operable breast cancer who were randomly assigned to mastectomy and oophorectomy on the same day, followed by tamoxifen therapy daily begun within 7 days. Follicular phase patients (A, n = 43; B, n = 38) (solid line) were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients (A, n = 55; B, n = 52) (dotted line) were defined as those reporting a last menstrual period 15–42 days from the time of surgery. Vertical error bars represent the 95% confidence intervals for the number of patients at risk at approximately 3 and 5 years. There was a statistically significant difference in the DFS curve for patients with ER-positive cancers ( $P = .04$ ) but not for those with ER-negative cancers ( $P = .09$ ).

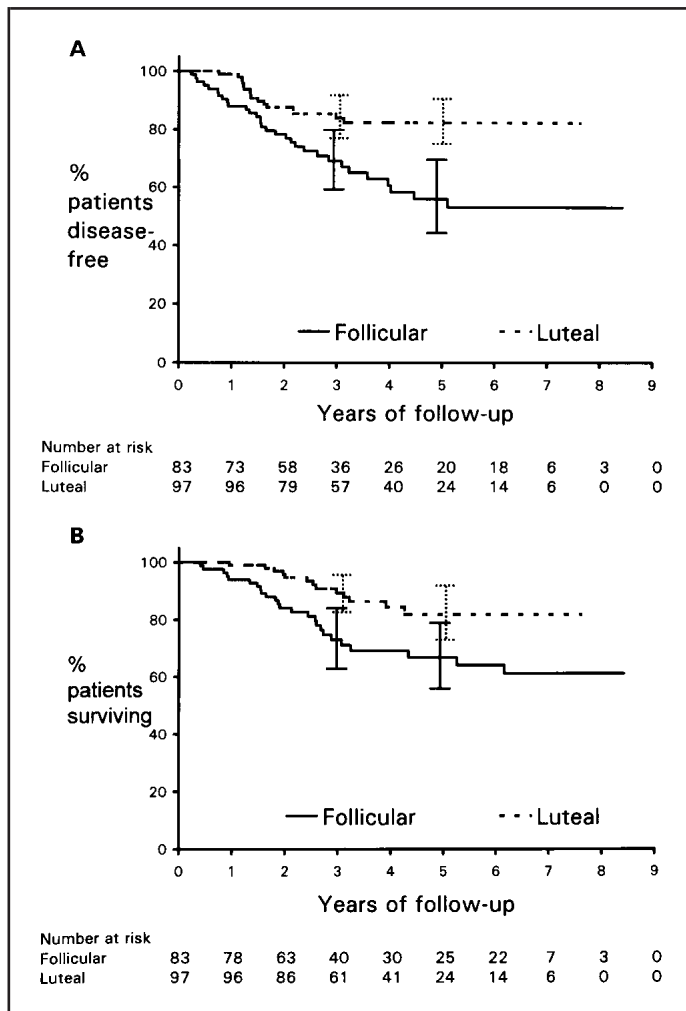
there may be a substantial anovulatory population (with unopposed but lower than follicular-phase estrogen levels) and a follicular population (with the follicular phase lasting longer than 14 days) included in the luteal phase groups in the main study samples. When the analysis was restricted to patients 44 years old and younger with a luteal phase of 15–35 days since the last menstrual period—circumstances likely to decrease the number of women with anovulatory, nonprogesterone-producing cycles included in the luteal phase group—the differences in the outcomes between the groups in the luteal and follicular phases increased (Fig. 6 and Table 2). The absence of hormone receptor data for one third of patients in the entire study led to small numbers in the hormone-receptor-positive and hormone-receptor-negative subsets. The study samples description (Fig. 1) shows that the study sample subsets 1, 2, and 3, on whom data are reported, are selected groups for whom the initial study



**Fig. 5.** Kaplan-Meier curves for disease-free survival (DFS) (A) and overall survival (OS) (B) patients younger than 45 years with operable breast cancer who were randomly assigned to the mastectomy and observation arm. Follicular phase patients (n = 91) (solid line) were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients (n = 95) (dotted line) were defined as those reporting a last menstrual period 15–35 days from the time of surgery. Vertical error bars represent the 95% confidence intervals for the number of patients at risk at 3 and 5 years. There was no statistically significant difference between the curves as determined by the log-rank test for DFS ( $P = .54$ ) and OS ( $P = .76$ ).

randomization cannot provide assurances regarding selection bias.

There are several strengths to the data reported in this study. First, the data were not confounded by oral contraceptive use (none used by our study patients), multiple surgeries, possible effects of mammography (none of the patients had mammography) and, most importantly, unspecified adjuvant therapies. Second, the date of the first day of the last menstrual period was available for all but 89 study subjects (Fig. 1). The four main study sample groups were defined by a pre-randomization variable—the first day of last menstrual period; thus, these groups should not be subject to selection bias. Statistical tests applied to these groups are therefore valid because of the randomization. The results of the multivariable analyses provide further assurances that the results from the main study sample groups are not explained by subtle differences in prognostic factors. Finally, the data from this study are internally concordant: the four intervention/menstrual cycle phase comparisons present a consistent pic-



**Fig. 6.** Kaplan-Meier curves for disease-free survival (DFS) (A) and overall survival (OS) (B) patients 44 years old or younger with operable breast cancer who were randomly assigned to mastectomy and oophorectomy on the same day, followed by tamoxifen therapy begun within 7 days. Follicular phase patients ( $n = 83$ ) (solid line) were defined as those reporting a last menstrual period 1–14 days from the time of mastectomy. Luteal phase patients ( $n = 97$ ) (dotted line) were defined as those reporting a last menstrual period 15–35 days from the time of surgery. Vertical error bars represent the 95% confidence intervals for the number of patients at risk at 3 and 5 years. There were statistically significant differences between the curves as determined by the log-rank test for DFS ( $P = .001$ ) and OS ( $P = .005$ ).

ture (Table 2); different definitions of the follicular and luteal phases of the menstrual cycle give qualitatively similar results; and the strength of the apparent benefit for patients having surgery during the luteal phase increases when likely anovulatory patients (women 45 years old and older) are excluded.

Our results do not address the impact of menstrual cycle phase at the time of mastectomy surgery in the same way as the results of the previous investigators did (14–16). In our study, the possible critical variables are the abrupt lowering of elevated estrogen and particularly progesterone levels as a result of oophorectomy at the time of breast cancer surgery. If the perimastectomy state is important, then our results support the Badwe et al. (13) hypothesis. However, it seems more likely that the impact of surgical oophorectomy is influenced by the phase of the menstrual cycle during which the surgery is performed. In normal breast tissue, epithelial cell proliferation and expression of prolactin receptors increase during the luteal phase of the

menstrual cycle (30). If such increases also occur in micrometastases, then the rapid lowering of hormonal levels by surgical oophorectomy during the luteal phase may exert a cytotoxic effect through a variety of mechanisms (31). In particular, differences in the regulation or levels of angiogenic factors and proteases between luteal and follicular phases may be important (32,33). Rapid changes in hormonal levels may also influence conditions within tissues that affect implantation of micrometastases (34). In this study, the similar levels of benefit of oophorectomy during the luteal phase seen in patients with ER-positive or ER-negative cancers suggest that an exaggerated hormone withdrawal response is not the major mechanism operating.

The results reported here are from *post hoc* analyses of a trial designed to address other primary objectives and, clearly, further investigations are needed to establish the possible mechanisms and to confirm the findings. The impact of other systemic adjuvant therapies (both chemotherapies and LHRH agonists) may similarly vary with initiation at different times during the menstrual cycle. Furthermore, the timing of the withdrawal of hormone replacement therapy in women found to have breast cancer may influence their long-term prognosis. Our results suggest a paradigm shift in breast cancer treatment from the current emphasis on the *type* of hormonal therapy used to greater emphasis on the characteristics of the patient and the tumor *when* hormonal therapy is begun. Because the levels of effect associated with oophorectomy are large, and because having surgery during the luteal phase is easily achieved, it is urgent that rigorous clinical trials be done to determine whether specifically performing definitive breast tumor excision surgery with simultaneous oophorectomy in the luteal rather than the follicular phase of the menstrual cycle is, in fact, beneficial and to investigate the mechanisms through which such observations operate. Studies of the impact of oophorectomy at different times in the menstrual cycle as a treatment for metastatic disease are also indicated by our results. In new trials, blood hormone assessments should be done to specify the biochemical phase of the menstrual cycle at the time of surgery, a protocol being followed in the National Surgical Adjuvant Breast Project/North Central Cancer Treatment Group (NSABP/NCCTG) N9431 (35). Finally, these results may have implications for the timing of therapies, particularly those of primary surgery, for other solid tumors.

In summary, we have found no evidence that the timing of mastectomy influences outcomes in women with operable breast cancer who received no adjuvant systemic therapy. By contrast, we found that women who underwent adjuvant oophorectomy simultaneously with mastectomy surgery during the estimated luteal phase of the menstrual cycle benefited from this treatment to a statistically significantly greater extent than did women who had this surgery during the follicular phase, and that women undergoing mastectomy and oophorectomy and tamoxifen during the follicular phase of the menstrual cycle derived a marginal benefit from the adjuvant hormonal treatment.

## REFERENCES

- (1) Beatson CT. On treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. *Lancet* 1896;2:104–7, 162–5.
- (2) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and

- 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1992;339:71–85.
- (3) Roche H, Mihura J, de Lafontan B, Reme-Saumon M, Martel P, Dubois J-B, et al. Castration and tamoxifen versus chemotherapy (FAC) for premenopausal, node and receptor positive breast cancer patients: a randomized trial with a 7 years median follow-up [abstract 134]. *Proc Annu Meet Am Soc Clin Oncol* 1996;15:117.
  - (4) Roche HH, Kerbrat P, Bonnetterre J, Fargeot P, Fumoleau P, Monnier A, et al. Complete hormonal blockade versus chemotherapy in premenopausal early-stage breast cancer patients with positive hormone-receptor and 1–3 node-positive tumor: results of the FASG 06 Trial [abstract 279]. *Proc Annu Meet Am Soc Clin Oncol* 2000;19:72a.
  - (5) Jakesz R, Gnatt M, Hausmaninger H, Samonigg H, Kubista E, Steindorfer P, et al. Combination goserelin and tamoxifen is more effective than CMF in premenopausal patients with hormone responsive tumors in a multicenter trial of the Austrian Breast Cancer Study Group [abstract 2]. *Breast Cancer Res Treat* 1999;57:25.
  - (6) Davidson N, O'Neill A, Vukov A, Osborne CK, Martino S, White D, et al. Effect of chemohormonal therapy in premenopausal node-positive, receptor-positive breast cancer: an Eastern Cooperative Oncology Group Phase III Intergroup trial (E5188, INT-0101) [abstract 249]. *Proc Annu Meet Am Soc Clin Oncol* 1999;18:67a.
  - (7) Bianco AR, Costanzo R, Di Lorenzo G, Adamo V, Altavilla G, D'Aprile M, et al. The Mam-1 GOCSI Trial: a randomized trial with factorial design of chemo–endocrine adjuvant treatment in node-positive early breast cancer [abstract 104]. *Proc Annu Meet Am Soc Clin Oncol* 2001;20:27a.
  - (8) Ratajczak HV, Sothorn RB, Hrushesky WJ. Estrous influence on surgical cure of a mouse breast cancer. *J Exp Med* 1988;168:73–83.
  - (9) Hrushesky WJ, Bluming AZ, Gruber SA, Sothorn RB. Menstrual influence on surgical cure of breast cancer. *Lancet* 1989;2:949–52.
  - (10) Gelber RD, Goldhirsch A. Menstrual effect on surgical cure of breast cancer [letter]. *Lancet* 1989;2:1344.
  - (11) Powles TJ, Jones AL, Ashley S, Tidy A. Menstrual effect on surgical cure of breast cancer [letter]. *Lancet* 1989;2:1343–4.
  - (12) Ville Y, Lasry S, Spyrtatos F, Hacene K, Brunet M. Menstrual status and breast cancer surgery [letter]. *Breast Cancer Res Treat* 1990;16:119–21.
  - (13) Badwe RA, Gregory WM, Chaudary MA, Richards MA, Bentley AE, Rubens RD, et al. Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. *Lancet* 1991;337:1261–4.
  - (14) Veronesi U, Luini A, Mariani L, Del Vecchio M, Alvez D, Andreoli C, et al. Effect of menstrual phase on surgical treatment of breast cancer. *Lancet* 1994;343:1545–7.
  - (15) Kroman N, Hojgaard A, Andersen KW, Graversen HP, Afzelius P, Lokdam A, et al. Timing of surgery in relation to menstrual cycle does not predict the prognosis in primary breast cancer. Danish Breast Cancer Cooperative Group. *Eur J Surg Oncol* 1994;20:430–5.
  - (16) Badwe RA, Bhansali MS, Vaidya JS. Unopposed oestrogen and survival of breast cancer. *Breast* 1998;7:66–71.
  - (17) Hanna N, Schneider M. Enhancement of tumor metastases and suppression of natural killer cell activity by beta-estradiol treatment. *J Immunol* 1983;130:974–80.
  - (18) Ervin PR Jr, Kaminski MS, Cody RL, Wicha MS. Production of mammatatin, a tissue-specific growth inhibitor, by normal human mammary cells. *Science* 1989;244:1585–7.
  - (19) Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor. *Cancer Res* 1979;39:3861–5.
  - (20) Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res* 1989;49:1996–2001.
  - (21) Fisher B, Saffer E, Rudock C, Coyle J, Gunduz N. Effect of local or systemic treatment prior to primary tumor removal on the production and response to a serum growth-stimulating factor in mice. *Cancer Res* 1989;49:2002–4.
  - (22) McCulloch P, Choy A, Martin L. Association between tumour angiogenesis and tumour cell shedding into effluent venous blood during breast cancer surgery. *Lancet* 1995;346:1334–5.
  - (23) Love RR, Duc NB, Allred DC, Binh NC, Dinh NV, Kha NN, et al. Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer. *J Clin Oncol*. In press 2002.
  - (24) Spiessl B, Beahrs OH, Hermanek P, Hutter RV, Scheibe O, Sobin LH, et al., editors. TNM Atlas: illustrated guide to the TNM/pTNM classification of malignant tumors. Berlin (Germany): Springer-Verlag; 1992. p. 359.
  - (25) Agresti A. Categorical data analysis. New York (NY): Wiley; 1990. p. 558.
  - (26) Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–70.
  - (27) Cox DR. Regression models and life-tables. *J Roy Statist Soc Ser B* 1972;34:187–220.
  - (28) Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
  - (29) Badwe RA, Wang DY, Gregory WM, Fentiman IS, Chaudary MA, Smith P, et al. Serum progesterone at the time of surgery and survival in women with premenopausal operable breast cancer. *Eur J Cancer* 1994;30A:445–8.
  - (30) Pike MC, Spicer DV, Dahmouh L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev* 1993;15:17–35.
  - (31) Hagen AA, Hrushesky WJ. Menstrual timing of breast cancer surgery. *Am J Surg* 1998;175:245–61.
  - (32) Heer K, Kumar H, Speirs V, Greenman J, Drew PJ, Fox JN, et al. Vascular endothelial growth factor in premenopausal women—indicator of the best time for breast cancer surgery? *Br J Cancer* 1998;78:1203–7.
  - (33) Thorpe SM, Rochefort H, Garcia M, Freiss G, Christensen IJ, Khalaf S, et al. Association between high concentrations of Mr 52,000 cathepsin D and poor prognosis in primary human breast cancer. *Cancer Res* 1989;49:6008–14.
  - (34) Solerte SB, Fioravanti M, Spinillo A, Ferrari E, Guaschino S. Association between hormonal and haemorheological changes during the menstrual cycle in healthy women. *Br J Obstet Gynaecol* 1988;95:1305–8.
  - (35) National Cancer Institute. National Surgical Breast and Bowel Project (NSABP) [cited 2001]. Available from: URL: <http://www.nsabp.pitt.edu>.

## NOTES

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