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Review

Timing of breast cancer surgery, menstrual phase, and prognosis: Systematic review and meta-analysis

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ABSTRACT

Background: For over 25 years, there has been a debate revolving around the timing of breast cancer surgery, menstrual cycle, and prognosis.
Methods: This systematic review synthesizes and evaluates the body of evidence in an effort to inform evidence-based practice. A keyword and reference search was performed in PubMed and Web of Science to identify human studies that met the inclusion criteria. A total of 58 studies (48 international and 10 U.S.-based) were identified. We provided a narrative summary on study findings and conducted a meta-analysis on a subset of studies where quantitative information was available.
Results: Findings from both qualitative and quantitative analyses were inconclusive regarding performing breast cancer surgery around a specific phase of the menstrual cycle.

Abbreviations: ND, no data; MR, medical record; LMP, last menstrual period; L, luteal; F, follicular; D, days; EF, early follicular; LF, late follicular; EL, early luteal; ML, middle luteal; LL, late luteal; PO, periovulatory; PM, perimenstrual; PR, proliferative; S, secretory; RO, reoccurrence; BF, breastfeeding.

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Conclusion: Based on the Institute of Medicine criteria, evidence is insufficient to recommend a change in current primary breast cancer surgery practice based on menstrual phase.

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1. Background

Scheduling breast cancer surgery in relation to the menstrual phase is an appealing treatment that relies on the body's own hormonal milieu and natural immunity. It is not toxic, invasive, nor likely to result in unwanted side effects, and could serve as a potentially simple and powerful therapeutic tool.

Nevertheless, 25 years of provocative experimental and clinical data are polarized regarding whether the luteal phase is more prognostically favorable than the follicular phase of the menstrual cycle when performing primary breast cancer surgery. Early studies demonstrated that premenopausal women with initial breast cancer have a significantly better prognosis when undergoing surgery in the luteal phase (Badwe et al., 1991a,b; Senie et al., 1991; Veronesi et al., 1994). Additionally, several studies noted deleterious consequences when primary breast cancer surgery was performed during the follicular phase (Saad et al., 1994a). Paradoxically, other studies reported a protective effect of undergoing surgery during the follicular phase (Macleod et al., 2000); albeit this may have been a consequence of patients being both peri- and postmenopausal (Ursin et al., 1995), or thin (Ryan, 1982). Conversely, opposing investigations found no relationship between menstrual timing of treatment for breast cancer and survival (Tsuchiya et al., 1996; Badwe et al., 1994; Powles et al., 1991a; Low et al., 1991; Ville et al., 1991; Rageth et al., 1991). To add to this dilemma, meta-analyses both refuted and advocated the influence of the menstrual period during surgery on breast cancer survival (Badwe et al., 2000; Mondini et al., 1997; Lemon and Rodriguez-Sierra, 1996; Fentiman and Gregory, 1993; Gregory et al., 1992). Currently, consideration of scheduling breast cancer surgery around the menstrual phase is deferred by surgical oncologists and patients until additional research is conducted.

The thought that the body's predictable biologic rhythms (i.e., chronotherapy) may be instrumental in treating breast cancer is alluring. An exhaustive review of all international and US studies was summarized, a meta-analysis was performed, and future recommendations were provided.

1.1. Existing literature

There are in total 8 meta-analyses and 3 systematic reviews that examined the relationship between breast cancer surgery and menstrual phase, with mixed findings. One meta-analysis of 37 published studies (n = 10,476) reported a modest survival benefit of 5% when surgery was performed in the luteal phase (Badwe et al., 2000). This study was based on publications until the year 2000. Only odds reductions were presented for each study with no additional details. The author did not distinguish the differences in outcome measures, thereby combining 5 year and 10 year survival, and 5 year and 10 year recurrence free survival (Badwe et al., 2000). Another meta-analysis of premenopausal breast cancer patients performed solely in Italy from 1977 to 1991, found no association for timing of surgery and survival using only one classification system based on the Badwe, Hrushesky and Senie criteria (Mondini et al., 1997). A US-based retrospective meta-analysis on 5353 premenopausal breast cancer patients, whose surgery was performed during the luteal phase (days 14–20) had an overall mean 5% benefit compared to those in the follicular phase. The risk of recurrence or death increased 5–6 fold after 10 years for women receiving surgery during days 7–14 of their cycle compared to those resected during days 21–36 (Lemon and Rodriguez-Sierra, 1996). In contrast, a meta-analysis of a subsample of 19 studies reported no difference in 5-year survival by treatment in different phases of the menstrual cycle. In this same meta-analysis, node positive cases demonstrated a better survival with progesterone larger than 1.5 ng/ml who underwent surgery during the luteal phase (Fentiman and Gregory, 1993). A final meta-analysis of 10 studies showed a significant overall effect of timing of surgery on 5-year survival rates. Patients who had needle biopsy during the unfavorable follicular phase (days 3–12) did worse than the remainder (Gregory et al., 1992). Findings from the eight meta-analyses revealed five studies in favor of the luteal phase. However, these retrospective meta-analyses were conducted ten or more years prior to the current study; limited only to patients residing in the US or Italy; restricted to one menstrual cycle classification system, and based on one combined prognostic outcome, rather than our six independent outcome categories.

The 3 systematic reviews reported disparate conclusions, and did not strongly or unanimously favor a specific phase of the menstrual cycle for breast cancer surgery. One review article by Chaudhry concluded that higher disease free survival and overall survival in patients occurred when surgery was performed during the luteal phase (Chaudhry et al., 2006b), while the other 2 reviews stated that evidence for the prognostic effect of timing of breast cancer surgery seems weak (Kroman, 2008); resulting in no difference in survival (Samuel et al., 2011).

The current meta-analysis is based on 25 years of research, encompasses both international and national studies, and contains both quantitative and qualitative analyses.

1.2. Biological mechanisms for the timing of breast cancer surgery

There are several hypotheses that might explain the effect of timing of surgery, addressing the influence of endocrine milieu or tumor handling and spread during surgery (Vasei et al., 2006). These findings have led to speculation that manipulation of the nodes or of the tumor during surgery might increase the seeding of micrometastases (Senie and Kinne, 2016; Fentiman et al., 1994). Physiologic change in the menstrual cycle might alter the probability of seeding through alterations in the behavior of tumor cells, immune cells, or cells at the settling site or through interactions between them. This could imply that appropriate pharmacological intervention at the time of breast carcinoma surgery might benefit survival (Harlap et al., 1998).

1.3. Estrogen and progesterone in the follicular and luteal phases

Unopposed estrogen in the follicular phase may enable more tumor emboli to escape and successfully establish micrometastases (Fentiman, 2002). In the follicular phase, estrogens reduce immune and phagocytic activity as well as circulating levels of interleukin-2 (IL-2), possibly increasing metastatic potential of breast cancer cells (Hrushesky et al., 1988). Simultaneously, estrogens also stimulate insulin-like growth factor which has a mitogenic effect on breast cells (Clarke et al., 1997; Dabrosin, 2003; Lavigne et al., 2004). In addition, angiogenesis is favored by highly circulating levels of

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