AN ABSTRACT OF THE THESIS OF

Margaret J. Phillips for the degree of Master of Science in Environmental Health presented on December 15, 1992.

Title: Premenstrual Syndrome and the Risk of Breast Cancer in Premenopausal Women.

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Annette M. Rossignol

A pilot study was conducted to evaluate whether premenstrual syndrome was a risk factor for breast cancer among premenopausal women. As subjects, 54 women between the ages of 26 and 46 years, each diagnosed with breast cancer, were compared to three separate control groups, consisting of 193 female patients seen in medical offices for routine physical exams, 51 female nursing students, and 559 female graduate students. Each eligible subject was either mailed or personally given a survey questionnaire probing premenstrual and menstrual symptomatology and general descriptive characteristics. An association between premenstrual syndrome and breast cancer was evaluated by estimating exposure odds ratios and associated confidence intervals. Analysis of the data suggested that premenstrual syndrome did not pose a breast cancer risk among premenopausal women.
Premenstrual Syndrome and the Risk of Breast Cancer in Premenopausal Women

by

Margaret J. Phillips

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Date thesis is presented December 15, 1992

Typed by B. McMechan for Margaret J. Phillips
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**General Characteristics of Subjects with PMS**

**General Characteristics of Subjects with PMS in Relation to Severity**

**PMS Exposure Odds Risk for Breast Cancer**

**Frequency of PMS Symptomatology Among Study Groups**
Premenstrual Syndrome and the Risk of Breast Cancer in Premenopausal Women

INTRODUCTION: THE NORMAL BREAST

Although breast tissue is present in both sexes, it is the female who undergoes radical changes starting with puberty, in pregnancies, and then through menopause, creating tremendous stress on normal breasts. Breasts consist of glandular tissue for milk production and secretion, as well as fibrous, adipose, lymphatic, circulatory, and nervous tissues. Most of the breast's bulk, except during lactation, is composed of adipose tissue. Glandular tissue forms the lobes and lobules which terminate into the alveoli and lactiferous ducts required for milk production (Warwick, 1973).

The breasts are controlled by the various reproductive hormones, with special emphasis on prolactin, estrogen, and progesterone. Normally, during the reproductive cycling, a female undergoes monthly changes in breast tissue size. However, normal breasts should not experience pain, lumps, or discharge (Berkow & Fletcher, 1987).
Breast Cancer

Until 1987, breast cancer was the leading cause of death in women, but currently it has been replaced by lung cancer as the number one leading cause of death among women. Breast cancer rates are increasing for women 55 years of age and older. Rates of developing breast cancer appear to be decreasing slightly in women under the age of 55 years (U.S. Department of Health and Human Services, 1988). The American College of Physicians claims that only 20 percent of breast malignancies occur in women under 50 years of age. Furthermore, only 0.2 percent of women develop breast cancer before the age of 25 (Haagensen, Bodian, & Haagensen, 1981). Post-menopausal women appear to be at highest risk for breast cancer (Berkow & Fletcher, 1987). Pre-menopausal women with functioning estrogen-progesterone hormonal cycles (see following chapter), a causal factor in premenstrual syndrome, were selected to be included in this pilot study. The purpose of this study was to evaluate premenstrual syndrome as a risk-factor to the onset of breast cancer. Review of the current literature has indicated that controversy still exists about the role of reproductive hormones with respect to breast cancer.
Common Types of Breast Cancer

Cancer In Situ

Cancers in situ are tumors, or masses, discovered at their original site of development. Cancers in situ are self-contained tumors which have not spread or metastasized into surrounding tissues, at the time of definitive diagnosis. Prognosis is better with cancers in situ than with invasive types of cancers. Most likely invasive cancer masses are not found at the primary site, but as a secondary metastasis from another area of the body (Berkow & Fletcher, 1987). Cancers can present with smooth margins, as in a benign disease such as fibrocystic disease. Quite often within the breast, small, well-defined, smooth masses with radioluscent halo of fat on these grams are indicative of benign tumors. In contrast, lesions with irregular contours and spiculated margins are the most common indicators of cancer (Winfield & Page, 1988).

Ductal cancers in situ are frequently found as microcalcifications (Winfield & Page, 1988). These are important diagnostic aids since the presence of calcifications...
indicates cellular necrosis causing calcification of those dead cells in the hypoxic centers of tumor masses. Yet, in 20 percent of the cases where calcifications are detected, these calcifications are present without any defined tumor (Mack, 1990).

Paget's disease affects the nipple and is associated with breast cancer. This disease characteristically presents as a reddened, crusty appearing nipple. An important clinical indicator of breast cancer, Paget's disease is usually invasive, a deep tumor mass sending Paget's cells up the tracts to the nipple. This disease is often associated with invasive masses. The deep, impalpable nature of the tumors causes a lengthy time before they can be diagnosed, allowing the tumors to grow (Berkow & Fletcher, 1987; Haagensen et al., 1983; Winfield & Page, 1988).

Lobular cancer in situ, is a slow-growing, generally painless mass involving the lobular units, the smaller units of the breast lobes that drain into the lactiferous ducts of the breasts. These cancers are generally hard to find in their early stages (Winfield & Page, 1988).

**Invasive Cancers**

From 60 to 70 percent of all breast cancers are invasive. These cancer cells are characterized by spreading freely throughout the tissue, rather than forming a self-contained tumor in situ (Agnew et al., 1965). Many lesions
have extensions of tissue beyond their basement, or foundation membrane. These tumors are not well-defined masses such as in situ forms of cancer. Invasive cancers are highly mitotic, rapid growing, and present the poorest prognosis. The cells of these cancers are so atypical that there is little concurrence as to their origin, other than categorization as invasive breast carcinoma, identified by the location in the breast (Winfield & Page, 1988).

There are some special types of invasive carcinomas that can be identified by their patterns on presentation to pathology. For example, mucinous cancers are little islands of cancer cells in pools of mucin, the main component of mucus. Medullary cancer can appear as smooth and rounded on diagnostic imaging, which could be misdiagnosed as a benign lesion. On dissection, large and irregular cancerous cells can be found within the tumor bathed in lymph and plasmacyte cells (Winfield & Page, 1988).

Infiltrating lobular cancers are diffuse, without a palpable mass, making them almost impossible to identify except by examining the breast for distortions and physical asymmetry (Winfield et al., 1988). Inflammatory cancer presents with a warm, erythematous, edematous, painful breast due to lymphatic involvement and is generally characterized by rapid tumor growth (Berkow & Fletcher, 1987).

Rare malignant tumors account for 5 percent of all breast cancers. Their compositions are of all types of
mixed cells, including sarcomas originating from anywhere within the body (Winfield & Page, 1988).

Recent research reported by the Harvard Medical School involved the examination of metastatic cancer by counting new microblood vessel growth in excised tumors. Not all tumors are capable of sending out tumor metastases, but in certain forms of invasive cancers there is a biologic process known as angiogenesis. New blood vessels develop in these tumors that can be used for identification of some virulent forms of cancers. Scientists indicate a 1.6 to 10.0 risk factor for a metastatic condition in each group of new vessels counted within the tumor ("Capillaries identify spreadable cancers," 1991).

Risks for Breast Cancer

Most precipitating factors for breast cancer are still largely unknown. Women are at highest risk for breast cancer. Pre-menopausal women between the ages of 35 to 39 years develop breast cancer at a rate of 572 times more often than in men. This figure shrinks to 34 times after the age of 85 years (Donegan, 1991).

Higher breast cancer incidence has been attributed to white women of higher socioeconomic classes, including women living in North America or northern Europe. Unmarried women, nulliparous (women without prior history of a viable pregnancy), with early onset menses and late menar-
che, and familial histories of the disease are also at risk (Kelsey & Gammon, 1991). However, in the United States, young premenopausal black women incident rates increased by 40 percent between 1947 to 1981. The rate for young white women showed a 13.7 percent increase over the same period of time (Krieger, 1990). Part of these apparent rate changes may have been affected by factors such as accurate reporting or access to health care. Jewish women and nuns appear to have a higher risk for breast cancer. Conversely, women from Asia and Africa, Japan, Mexican-Americans, and American Indians all appear to be at lower risk (Kelsey & Gammon, 1991).

Familial history with primary relatives, including mothers and/or sisters with a premenopausal history of breast cancer, translates to an increased probability of earlier onset breast cancer for the patient, prior to age 40, and to a greater risk of bilateral breast cancer (Anderson, 1992; Lynch & Watson, 1990; Mettlin, Croghan, Natarajan, & Lane, 1990; Roseman, Straus, & Shorey, 1990). These findings are consistent with many published studies of the effects of first-degree familial risk, shown in areas of high and low breast cancer incidence areas geographically, and are estimated to account for over 10 percent of the breast cancer cases in women under the age of 45 years (Parazzini, La Vecchia, Negri, Francechi, & Bocciolone, 1992). Parazzini et al. also raised the question of which mechanisms are at play concerning mother and/or
sister breast cancer risks. These findings were in conformance with those previously established by Mettlin et al. in 1990. Both studies questioned whether breast cancer in young women could be an inherited tendency, or an inherited susceptibility to certain risk factors, including environmental risk factors. This would include, for instance, women exposed to the same environmental effect living in close proximity.

The area of genetic research has been focused upon reports specific to the premenopausal breast cancer-heredity link. Researchers have divided cancer into two categories, familial-linked breast cancers and wild, or sporadically induced, cancers (Anderson, 1992). In the familial category, there have been four inherited types of breast cancer associated with early onset, premenopausal, and bilateral inclusion.

The Li-Fraumeni syndrome, thought to be associated with breast cancers in women under 35 years of age, has been suspect in other forms of tumors within families, especially sarcomas and brain tumors. The Li-Fraumeni syndrome has been linked to a dominant, inherited gene mutation found on the p53 gene of the 17th chromosome (Anderson, 1992; Barnes et al., 1992; Skolnick & Cannon-Albright, 1992). Cowden disease is a rarer form of inherited breast cancer. It has been reported that 90 percent of the female carriers have breast tumors and that approximately 50 percent of those women develop breast cancer.
(Anderson, 1992). However, most commonly breast cancer develops as an in situ disease associated with a close relative also diagnosed with breast cancer, also known as the familial-link risk factor. The fourth type of inherited tumor, lined by studies to either the 8th or the 17th chromosome, but as yet unconfirmed, is the type of cancer associated with breast cancer and ovarian cancer (Anderson, 1992; Lynch & Watson, 1990).

Breast cancer among patients without any close relatives who have experienced the disease has been undergoing greater scrutiny lately. Anderson (1992) theorizes genetic mutations cause a tumor-suppressing gene to cease functioning, allowing abnormal cells to proliferate. Specifically, the p53 tumor-suppressor gene on the 17th chromosome has been isolated. This gene has been associated with a genetic predisposition to some forms of hereditary breast cancers (Levine, 1992; Malkin et al., 1992; Shields et al., 1991; Skolnick & Cannon-Albright, 1992; Toguchida et al., 1992). Through these mutated p53 genes, mutated proteins are produced that accumulate within the tumor cell in larger amounts than their normal counterparts. These mutated proteins encourage the cells to grow more efficiently (Levine, 1992).

In addition, studies have supported long-term, low dosage ionizing radiation as used in chest x-rays and fluoroscopy, and the radiation in massive exposures such as the atomic blasts on Japan, in direct relation to the increase

Research has even suggested nitrogen dioxide, a component in smog, as a possible influence on breast cancer promotion. Nitrogen dioxide impairs the ability of killer T-cells to attack any tumor cells circulating in blood vessels after breaking off the primary tumor site. This impairment of the T-cells enhances metastases (Fackelman, 1990).

Pesticides constitute another area of environmental research in their potential for promoting breast cancers (Falck, Ricci, Wolff, Godbold, & Deckers, 1992). Unfortunately, the study samples considered were too small to conclusively correlate the exposure of certain pesticides to breast cancer. However, increased concentrations of certain pesticides were found in the tumor samples, but the researchers were unable to determine if the accumulations were as a result of the disease or were a causal factor.

High fat diets, in which fats constitute more than 30 percent of total daily intake, have been receiving tremendous attention (Cohen, 1987). The associations have been weak, however, whereas possible confounders have been high. One study found that fatty foods directly affect estrogen levels (Raloff, 1990). The United States, Britain, and the Netherlands have high fat diets and the highest breast cancer rates. Japan, Singapore, and Romania consume low fat diets and show from 1/6 to 1/2 the breast cancer rate
of the United States (Wallis, 1991). Migration studies show breast cancer incidence rises with diet changes to a higher fat content. Breast cancer has risen 58 percent in a five-year study of Japanese women as they westernize and consume more fat (Cohen, 1987; Kelsey & Gammon, 1991). In recent studies, higher than normal HDL levels have been indicated as a factor in the increase of the risk of breast cancer in women. Higher HDLs reduce the risk of cardiovascular disease, but may stimulate growth of tumor cells in breast cancer (Willett et al., 1991).

Alcohol consumption of 5g or more per day has been implicated in breast cancer studies. However, flawed study designs have begged the question of the accuracy of self-reported drinking habits and the environments in which subjects consumed their drinks, such as smoke-filled taverns (Schatzkin et al., 1987; Willett et al., 1987). Studies show a weak positive link between cigarette smoking and breast cancer, including passive smoking (Palmer et al., 1991; Wells, 1991).

Nulliparity, another suspected risk factor, has been theorized to be due to long uninterrupted blood levels of estrogen, especially if combined with early onset of menses (Yoo et al., 1992). Conversely, bilateral oophorectomy early in the premenopausal stage decreases the risk of breast cancer development (Kelsey & Gammon, 1991). Reports have been published to the effect that prolonged breast feeding, from seven to nine months, may also protect
against breast cancer (Yoo et al, 1992). However, the hormonal influence on breast cancer remains a matter of dispute among a number of researchers (Donlin-Shore, 1991). Support for hormonally-induced breast cancer remains strong due to observations which have demonstrated reduced breast cancer risk after removal of both ovaries, and by cancer growthstimulation in the presence of estrogen. These associations, however, may have been confounded by such factors as tissue changes, immunological changes, environmental influences, or early detection.

The issue of tumor receptors is another aspect of the hormone debate. Breast cancer tumors without estrogen uptake are known as negative estrogen receptors. When compared to estrogen containing tumors, negative estrogen tumors are larger and are more unstable due to increased proliferation ability. Compared to estrogen positive receptor tumors, negative estrogen tumor breast cancer has evidenced decreased remission periods and is characterized by a decreased survivor rate (Stanford & Greenberg, 1989). An association between reproductive hormones, including exogenous estrogen and breast cancer, has yet to be proven (Rich, Hager, & Furmanski, 1983; Winfield & Page, 1988).

Amidst the controversy of breast cancer risk, and hormonal influences on that risk, are two recently reported studies. One study conducted in northern Italy looked at menstrual and reproductive factors concerning familialy-related breast cancer (Parazzini et al., 1992). Reproduc-
ative factors compared were parity, abortions, age at first birth, ages at menarche and menopause, and lifetime menstrual patterns. The study was conducted over seven years, between 1983 and 1990, selecting approximately 5,000 eligible subjects for a case-control study. Each subject was interviewed in person. Roughly one-third of the subjects were under the age of 45 years. Unfortunately, the results were not reported by age, only by reproductive patterns and certain socioeconomic classes. The researchers concluded there was no discernible risk to familial breast cancer owing to reproductive and hormonal influences.

The second study was conducted in the then United Soviet Socialist Republic among three ethnic groups, Moldavians, Ukrainians, and Russians, comparing reproductive risks with respect to breast cancer (Pikhut & Levshin, 1988). The reproductive factors considered were menstrual patterns, age of onset and cessation of menstruation, sexual activity, parity patterns and ages at first and last birth, lactation, and premenstrual syndrome. In this case-control study, 1,175 women were interviewed by a single interviewer. Problems with bias were acknowledged when comparing three different ethnic groups and their differences in lifestyles, diets, and social patterns. Potential bias could have been addressed by the use of a single interviewer during the data collection stage. The tables were not stratified by age, nor did the authors identify what methods they used to analyze their data. The confounding
factor of family history specific to reproductive cancer was not addressed within these ethnic groups. How these subjects were chosen was not indicated, other than indicating their breast cancer status. This study found a risk of breast cancer associated with premenstrual syndrome, OR = 2.4 for urban Moldavians, 2.6 for rural Moldavians, 8.7 for urban Ukranians, 3.3 for urban Russians, and 13.6 for rural Russians. For these figures, the level of confidence was not reported.

In conclusion, continuing research has been indicated in all areas of breast cancer research, with chromosomal and genetic involvement appearing to be the most promising areas of inquiry.
Introduction

Breast cancer, while relatively rare in premenopausal women, is the second leading cause of cancer death in women in the United States (Kelsey & Gammon, 1991). Hormonal influences relating to breast cancer risk remain unproven since testing for the various circulating hormones have not been adequate and are very costly (Stanford & Greenberg, 1989).

Premenstrual syndrome (PMS) remains a controversial issue among many factions of the health community (Rossignol & Phillips, 1992) (Appendix A). Studies of potential contributors which exacerbate PMS compose an extensive scientific literature (Harlow & Matanoski, 1991), and exercise an effect upon the medical community's attitudes and treatment preferences. While the various symptomatology comprising this syndrome has been investigated extensively, few reports have examined the relationship of PMS to the occurrence of reproductive cancers such as breast cancer (Boyle, Berkowitz, & Kelsey, 1987). Prior to the present study, only one other investigation studied PMS in relation to breast cancer (Pikhut & Levshin, 1988).
Undertaken in Russia, the investigators studied reproductive function, and in addition found a positive link between PMS and the development of breast cancer. This study found an increased risk of breast cancer associated with premenstrual syndrome, reporting OR ratios of 2.4 for urban Moldavians, an 2.6 among rural Moldavians, 8.7 for urban Ukranians, 3.3 for urban Russians, and 13.6 for rural Russians.

The purpose of this pilot study was to survey premenopausal women recently diagnosed with breast cancer. These women were compared to three different control groups to determine if there was any excess risk of breast cancer associated with PMS.

Research Methods

This pilot study, conducted at Oregon State University in Corvallis, Oregon, selected 66 eligible women from two Oregon clinics specializing in breast diseases. One clinic was located in a semi-rural setting. The other office was located in a suburb of a larger metropolitan area. Both clinics were operated by the same physician. Each subject was selected based on the following criteria: Women who had experienced a recent, positive diagnosis of breast cancer before reaching menopause, who were currently menstruating or within a year of cessation due to chemother-
apy, who were between the ages of 20 to 50 years, and who had no history of a complete hysterectomy.

Each subject was mailed a questionnaire requesting participation with a cover letter detailing the voluntary nature of the inquiry and assuring the anonymity of their responses (Appendix B). The questionnaire probed for premenstrual symptomatology, menstrual discomforts, for surgical procedures, medications, term pregnancies, and for general information, including age, height, and weight. The premenstrual symptoms listed on the form focused common complaints. These complaints included headache, bloating and weight gain, acne, depression, irritability, tiredness, cravings for salty or sweet foods, binge eating, and breast swelling and tenderness. An "other symptoms" category was also included. The symptoms were ranked by the participant on the basis of mild, moderate, or severe. To differentiate premenstrual from menstrual symptoms, a question was included asking the number of days before menses onset that premenstrual symptoms occurred.

Of the 66 total surveys mailed, 57 of the women responded by returning the questionnaires (i.e., 86% rate of response). Three mailings were duplications since some patients had been seen at both clinics. Nine of the subjects chose not to participate in the study. Three surveys were subsequently eliminated from the study due to self-disclosure of complete hysterectomies with the removal of both ovaries and fallopian tubes.
The control group data were selected from two previous studies conducted at Oregon State University between 1985 and 1990 by Rossignol and Bonnlander (1990, 1991). Subjects for these studies were chosen based upon the same selection criteria as the breast cancer patients, with the exception that these subjects did not have breast cancer. The data consisted of 193 routine medical exam patients from seven local obstetrical/gynecological offices, 559 graduate students from O.S.U., and 51 nursing students in their first year of nursing school. Similar to the subjects of the present study, the controls were either mailed or personally handed a questionnaire. The response rate varied among the controls. The graduate student study, in 1988, had a 61 percent response rate: Of 1,419 eligible students receiving the questionnaire, 869 were returned after two mailings. Of those responses, 559 women between the ages of 24 and 53 years met the study requirements, based on active, regular menstruation.

The subjects recruited from physician offices were given questionnaires by their physicians. The unpublished results of the study (Rossignol & Bonnlander, 1991) states that the manner in which the patients were given these surveys varied, depending on the administering physician. Some physicians made sure that each eligible woman received one while others did not. Response bias was assessed by comparing the data obtained from the doctor who gave all the eligible women questionnaires to those of physicians
using variable systems, finding no difference among the responses. Of 284 eligible women, the results from 91 women seeking specific medical treatment were not considered in the present survey since the existence of breast cancer was difficult to ascertain from the data available. Only the 193 women visiting physicians for routine physical exams were included for purposes of data analysis.

The survey was given to each nursing student by an instructor, completed by the student, and then returned to the instructor during class (Rossignol & Bonnlander, 1990). The exact response rate is unknown, but almost the entire class was reported to have submitted completed forms to the instructor (n=73). Of the total number of forms submitted, 22 were eliminated from data analysis because they failed to meet the study admission criteria.

The survey form used for the cases was almost identical to the form used for the controls. The only difference between the questionnaires pertained to a question included for the control groups about major areas of concentration in their college studies, if they were among the two student groups, or the reason for their visit if they were a medical patient. A question referring to the participant's willingness to be interviewed in person was deleted on the breast cancer patients' surveys. A question was added to the case group questionnaire inquiring whether the respondents had changed their dietary habits since their cancer had been diagnosed. In this pilot study, to enhance compa-
rability and prevent bias, every effort was made to closely follow the exact format for data collection used in each of the prior studies (Rossignol & Bonnlander, 1990, 1991).

Once the data were collected, a computer-generated statistical analysis program, the Statistical Package for the Social Sciences (SPSS/PC+), was used to analyze the information. Each of the three control groups was compared to the breast cancer case group to examine any potential risk PMS may present in relation to breast cancer. The exposure odds ratios were estimated, and chi-square analysis was used to estimate variances (Hennekens & Buring, 1987). Each group was then stratified by age to ascertain possible effect modification by age. The crude exposure odds ratios within each control group were compared to the age-stratified pooled exposure odds ratios for further examination of potential age confounding.

Finally, a PMS score was calculated in accordance with techniques previously used (Rossignol & Bonnlander, 1990). Those subjects identifying themselves as PMS sufferers on a regular basis were evaluated. The individual symptom was tallied as 1 for a reply of mild, 2 for moderate, or 3 for severe, for a potential maximum of 36. The actual numbers for the combined group ranked from 0 to 32). This scoring allowed for comparison of PMS symptomatology among the study groups.
Results

The general characteristics of each group of subjects regularly suffering PMS are shown on Tables 1 and 2. The median age of graduate students experiencing PMS regularly was 31 years, the median age for the nursing students with PMS was 31.5 years, and the group of patients for routine medical exams were older, at a median age of 35 years. The breast cancer patients were the oldest group with a median age of 42 years. The graduate students had fewer term pregnancies than the other three groups, with a median number of 0. The nursing students, patients for routine medical exams, and the breast cancer patient group had a median number of 2 term pregnancies, whereas the breast cancer patients had a median number of 1 term pregnancy. Conversely, the graduate students presented the widest range of overall PMS scores at a range of 3 to 32. The other groups were 4 to 28 for student nurses, 3 to 31 for the routine exam patients, and 0 to 30 for the breast cancer patients. The graduates and cancer patients each showed PMS symptom median scores of 11 points overall, while the combined severity of student nurses and routine exam patients ranked higher at, respectively, median scores of 16 and 15. The most frequently reported PMS symptoms are listed in Table 1. The complaint of irritability was the most frequently reported general symptom.
<table>
<thead>
<tr>
<th>Subjects with PMS</th>
<th>Age (years)</th>
<th>Term Pregnancies (number)</th>
<th>PMS Score</th>
<th>Symptom Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graduate Students (n=321)</td>
<td>Range = 24-52 (median = 31)</td>
<td>Range = 0-5 (median = 0)</td>
<td>Range = 3-32 (median = 11)</td>
<td>Irritability = 85% Breast swelling &amp; tenderness = 85% Bloating &amp; weight gain = 85%</td>
</tr>
<tr>
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<td>Age 40 or less = 85% Age 30-50 = 58%</td>
<td>One or more = 26%</td>
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<tr>
<td>Nursing Students (n=36)</td>
<td>Range = 24-45 (median = 31.5)</td>
<td>Range = 0-4 (median = 2)</td>
<td>Range = 4-28 (median = 16)</td>
<td>Irritability = 94% Tiredness = 89% Depression = 83% Bloating &amp; weight gain = 83%</td>
</tr>
<tr>
<td></td>
<td>Age 40 or less = 92% Age 30-50 = 56%</td>
<td>One or more = 64%</td>
<td></td>
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<tr>
<td>Routine Exam Patients (n=156)</td>
<td>Range = 25-51 (median = 31.5)</td>
<td>Range = 0-5 (median = 2)</td>
<td>Range = 3-31 (median = 15)</td>
<td>Irritability = 93% Bloating &amp; weight gain = 90% Breast swelling &amp; tenderness = 83%</td>
</tr>
<tr>
<td></td>
<td>Age 40 or less = 76% Age 30-50 = 83%</td>
<td>One or more = 81%</td>
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<tr>
<td>Breast Cancer Patients (n=41)</td>
<td>Range = 32-46 (median = 42)</td>
<td>Range = 0-5 (median = 2)</td>
<td>Range = 0-5 (median = 11)</td>
<td>Irritability = 78% Bloating &amp; weight gain = 90% Binge eating = 63% Breast swelling &amp; tenderness = 63%</td>
</tr>
<tr>
<td></td>
<td>Age 40 or less = 29% Age 30-50 = 100%</td>
<td>One or more = 68%</td>
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Table 2. General Characteristics of Subjects with PMS in Relation to Severity.

<table>
<thead>
<tr>
<th>Subjects with PMS</th>
<th>Symptom Frequency by Severity</th>
<th>PMS Prior to Menses (average by no. days)</th>
<th>Menstrual Symptoms (mild to severe)</th>
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<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
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<tr>
<td></td>
<td>Depression = 46%</td>
<td>Breast swelling &amp; tenderness = 40%</td>
<td>Craving sweets = 14%</td>
</tr>
<tr>
<td></td>
<td>Bloating &amp; weight gain = 44%</td>
<td>Irritability = 39%</td>
<td>Breast swelling &amp; tenderness = 11%</td>
</tr>
<tr>
<td></td>
<td>Acne = 44%</td>
<td>Bloating &amp; weight gain = 35%</td>
<td>Irritability = 11%</td>
</tr>
<tr>
<td></td>
<td>Tiredness = 44%</td>
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<td>Graduate Students</td>
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<td>(n=321)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing Students</td>
<td>Bloating &amp; weight gain = 47%</td>
<td>Irritability = 44%</td>
<td>Irritability = 31%</td>
</tr>
<tr>
<td>(n=36)</td>
<td>Acne = 47%</td>
<td>Tiredness = 42%</td>
<td>Breast swelling &amp; tenderness = 22%</td>
</tr>
<tr>
<td></td>
<td>Depression = 39%</td>
<td>Binge eating = 39%</td>
<td>Tiredness = 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Craving sweets = 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety = 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine Exam Patients (n=156)</td>
<td>Acne = 46%</td>
<td>Irritability = 42%</td>
<td>Craving sweets = 24%</td>
</tr>
<tr>
<td></td>
<td>Depression = 44%</td>
<td>Anxiety = 38%</td>
<td>Irritability = 22%</td>
</tr>
<tr>
<td></td>
<td>Tiredness = 35%</td>
<td>Tiredness = 37%</td>
<td>Binge eating = 19%</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer Patients (n=41)</td>
<td>Bloating &amp; weight gain = 32%</td>
<td>Irritability = 34%</td>
<td>Craving sweets = 27%</td>
</tr>
<tr>
<td></td>
<td>Acne = 32%</td>
<td>Headache = 34%</td>
<td>Irritability = 24%</td>
</tr>
<tr>
<td></td>
<td>Depression = 29%</td>
<td>Breast swelling &amp; tenderness = 34%</td>
<td>Tiredness = 20%</td>
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</tbody>
</table>
Table 2 lists the most commonly reported symptoms by severity. The mild category indicated no single outstanding symptom, but acne was in the top three listings for all of the study groups. In the moderate column, irritability frequently appeared in the first or second position. The most frequent complaint in the severe category was either irritability or craving sweets, both appearing as one the three most commonly complained of symptoms for all four study groups. The number of days PMS symptoms appeared on average prior to the onset of menstruation is also indicated in Table 2. The student nurse range was from 2 to 12 days, the graduate student range was 0 to 14 days, and the cancer patient range was 2 to 14 days. The routine exam patient range was the longest, at a maximum of 16 days before menstruation onset each month.

The median number of seven days was consistent for all four groups. However, the nurses experienced the greatest number of days before menses onset, with 39 percent noticing symptoms greater than the seven day median. The graduate student group results indicated that 25 percent experienced symptoms earlier than seven days before menstruation onset, whereas 37 percent of the routine exam patient group and 30 percent of the breast cancer patient group experienced PMS symptoms before the seven day median. The last column in Table 2 shows the severity of menstrual symptoms either with or without PMS, and the effect of these symptoms upon the work patterns of the subjects. Again, the
nursing students ranked their menstrual severity the highest with for both conditions, whereas 85 percent of the breast cancer patients experienced no PMS symptoms. However, at the same time the presence of menstrual symptoms severe enough to affect their work was highest among the breast cancer patients.

Examination of the crude exposure odds ratios for PMS as a potential risk factor for breast cancer is listed in Table 3. The graduate student group showed a crude exposure odds rate of 2.2 (90% confidence level for 1.3 to 3.6), the nursing student group showed a crude exposure odds ratio of 1.3 (90% confidence level for 0.6 to 2.7), and patients seen for routine medical exams showed the lowest crude ratio at 0.8 (90% confidence interval for 0.4 to 1.4).

Table 3 also presents a control group stratification by age groups. An increased exposure odds ratio for each of the 41 to 50 years age level among the control groups, compared to the 20 to 40 years category, was consistent with an increased risk of breast cancer with increasing age. As shown in Table 4, the breast cancer case group showed that 76 percent of the sample population suffered PMS regularly. The corresponding percentage for the control group of patients seen for routine medical exams was higher at 81 percent of the sample population with PMS. The graduate student group was ranked lowest at 57 percent, with nursing students reported at 71 percent.
Conclusions

The exposure odds ratio for graduate students over the age of 41 years appeared to indicate an increased risk of breast cancer with exposure to premenstrual syndrome, and a slight preventive effect among the patients for routine exams. However, considered jointly, the data do not support a risk of breast cancer in the presence of PMS. The stratified age groups listed in Table 3, specifically the relatively wide confidence intervals, suggest that the sample size for the breast cancer group was not sufficiently large to precisely estimate relatively minor increase factors. Some confounding by age was evident when the crude exposure odds ratio was compared to the pooled

Table 3. PMS Exposure Odds Risk for Breast Cancer.

<table>
<thead>
<tr>
<th>Description</th>
<th>Nursing Students</th>
<th>Graduate Students</th>
<th>Routine Exam Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude Ratio Ages 20-40</td>
<td>1.31 (0.63-2.73)</td>
<td>2.20 (1.29-3.75)</td>
<td>0.75 (0.41-1.37)</td>
</tr>
<tr>
<td>Ages 41-50+</td>
<td>1.21 (0.16-9.24)</td>
<td>2.19 (0.95-4.41)</td>
<td>0.95 (0.87-1.04)</td>
</tr>
<tr>
<td>Pooled Ages</td>
<td>1.11 (0.99-1.12)</td>
<td>1.90 (0.85-4.24)</td>
<td>0.74 (0.45-1.22)</td>
</tr>
<tr>
<td>Pooled Groups</td>
<td></td>
<td></td>
<td>1.39 (0.99-1.97)</td>
</tr>
</tbody>
</table>

Table 4. Frequency of PMS Symptomatology Among Study Groups.

<table>
<thead>
<tr>
<th>Description</th>
<th>Graduate Students</th>
<th>Nursing Students</th>
<th>Routine Exam Patients</th>
<th>Breast Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMS, Yes</td>
<td>321 @ 57</td>
<td>37 @ 71</td>
<td>156 @ 81</td>
<td>41 @ 76</td>
</tr>
<tr>
<td>PMS, No</td>
<td>224 @ 40</td>
<td>15 @ 29</td>
<td>37 @ 19</td>
<td>13 @ 24</td>
</tr>
<tr>
<td>Totals</td>
<td>559 @ 100</td>
<td>51 @ 100</td>
<td>193 @ 100</td>
<td>54 @ 100</td>
</tr>
</tbody>
</table>
exposure odds rate within each control group. However, the age-stratified odds ratio for each group showed little effect modification by age. For example, the nursing students control group crude exposure odds ratio of 1.3, compared to the pooled age category of 1.1, indicates slight confounding by age. However, the age-stratified groups of 1.0 for the 20 to 40 years level and 1.2 for the 41 to 50 years level indicated little modification by age. The wide confidence intervals (0.16-9.24) for the 41 to 50 years age group, for example, suggested a random error, probably due to the small sample size.

The graduate student group was larger (n=559), a factor which contributed to a narrower confidence interval for the crude exposure odds rate of 2.2 (90% confidence interval for 1.3-3.8). However, the confidence level increased when the graduate student group was stratified by age and then pooled, as shown in Table 3.

The control group most similar to the breast cancer cases were patients seen for routine medical exams. The median age of this control group was 36 years, compared to a median age of 42 years for the breast cancer group. A large sample size (n=193) for the routine medical exam patient control group allowed a comparison ratio of 3.6:1.0 to the breast cancer patient group (Table 2). The exposure odds ratios for the routine medical exam patient group were similar to the crude exposure odds ratios and the pooled odds ratio provided little indication of confounding by
age. The age-stratified figures also indicated there was no effect modification. A crude OR of 0.8 (90% confidence interval for 0.4 to 1.4) and the pooled OR for the two age groups of 0.7 (90% confidence interval for 0.5 to 1.2) appeared to show a slight indication of preventive effect, but could also be reasonably be explained by random variation.

The self-ranking method used for this type of survey contains a potential bias since pain perception among the subjects may not be consistent since pain threshold tolerance is individual in nature. Increased physical awareness among the breast cancer patients may heighten the need to take better care of themselves, influencing how they respond to PMS and to menstrual symptoms with respect to daily activities. Patients surviving a life-threatening disease such as breast cancer may differ in perspective with regard to PMS symptoms and their physical well-being when compared to the control group subjects.

A possible source of error could be attributed to the brief description of PMS in the questionnaire. It may be speculated that subjects perhaps misunderstood the differences between PMS and menstrual symptoms. To control for recall bias among the breast cancer patients, only recently diagnosed patients were eligible, and those reporting on their patterns prior to diagnosis were screened for recent histories. As reported above, three women reported on their PMS patterns before undergoing complete hysterecto-
mies, but the surveys were discarded due to the length of post-operative time which had passed.

Another potential error deals with certain drug therapies for breast cancer, which can suppress ovarian function. Although the question was asked whether the patient was taking any drugs, nothing was asked of past drug history. Two cancer patients reported ovarian suppression causing a cessation of menstruation, yet listed PMS symptoms. Since the exposure odd ratios among the different control groups were within such close range, bias and confounding appeared to be minimal.

The power of this study and its variability presented problems due to the small sample population size of pre-menopausal breast cancer cases. A larger sample population may be indicated to determine if there is a relationship between PMS and breast cancer, especially given the lack of documented evidence in this area of inquiry.
BIBLIOGRAPHY


APPENDICES
Appendix A

Modes of Treatment for PMS
Obstetricians’ and Gynecologists’ Beliefs and Preferred Modes of Treatment for Women Diagnosed with Premenstrual Symptoms

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Corvallis, Oregon

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Abstract
This study found substantial differences among obstetricians and gynecologists in their beliefs about the etiology of and preferred modes of treatment for premenstrual symptoms.

Premenstrual syndrome (PMS) is an array of symptoms that occurs or is aggravated during the late luteal phase of the menstrual cycle. The symptoms typically include depression, anxiety, irritability, breast swelling and tenderness, water retention, headaches, and food cravings, although well over 100 symptoms have been reported to be associated with the premenstrual phase of the menstrual cycle. Several investigators have reported that the term “premenstrual syndrome” is a misnomer in that the “syndrome” in fact is comprised of several distinct syndromes, some of which consist primarily of physical ailments whereas others consist of emotional or psychological symptoms; other investigators find no reproducible subclassifications of PMS.

Putative causes of PMS include a wide variety of psychological, biochemical, and lifestyle factors, including a deficiency of progesterone and an excess of estrogen; deficiencies in prostaglandins, vitamins (especially vitamin B₆, deficiency), and/or magnesium; hypoglycemia; fluid retention; an excess of prolactin; an allergy to one’s own hormones; endorphin deficiency or abnormality; stress; psychiatric disorder; lack of exercise; caffeine; high sodium intake; alcoholic beverage use; a diet high in sugar and refined sugar; and variation in daily hours of sunlight (PMS and seasonal affective disorder have
been reported to be related.\cite{9,10} Few conclusive data exist, however, to support a causal role for any of these factors. The data that do exist tend to come from small case studies (fewer than 30 subjects) with attendant problems of lack of precision and statistical power.\cite{9,10}

Given the lack of consistency in the PMS literature, it seems possible that substantial variability in beliefs about PMS and preferred modes of treatment for women diagnosed as having PMS might exist among practicing obstetricians and gynecologists.\cite{10} The objective of this study was to assess the extent of any such variability, with particular emphasis on whether differences in beliefs or preferred modes of treatment vary according to the age or sex of practicing obstetricians and gynecologists.

**METHODS**

The study was conducted in the state of Oregon. Eligible physicians were the 351 physicians registered by the Oregon Board of Medical Examiners as certified to specialize in obstetrics and/or gynecology in Oregon.

Each eligible physician was mailed a questionnaire soliciting information about medical practices concerning PMS and about the physician's assessment of the major precipitating factors for PMS onset. Physicians were asked to rank the top five in a list of 13 putative precipitating factors for PMS onset (age, caffeine, childbirth, depression, sugar intake, sodium intake, hormonal imbalance, lack of exercise, low pain threshold, psychological difficulties, variation in hours of sunlight, self-preoccupation, and stress) and to check as many of the preferred modes of treatment as were relevant. To reduce the likelihood that the physicians would suspect our interest in comparing responses according to age and sex, information about the age and sex of each physician was ascertained from a listing provided by the Oregon Board of Medical Examiners.

Two hundred thirty (66%) of the physicians returned questionnaires after two mailings. Six of the respondents subsequently were found not to be certified to specialize in obstetrics and/or gynecology in Oregon and were excluded from the data analysis. This exclusion left data on 224 obstetrician and/or gynecologist specialists for analysis. The questionnaires for 12 of these 224 respondents had missing information; these questionnaires were included in the data analysis for questions for which answers were available. The study physicians ranged in age from 28 to 86 years. Twenty-seven percent of the physicians were women.

The data were analyzed by sex and by two age categories (less than 40 years old and age 40 years or older). The age categories were determined partly on the basis of observed differences in responses according to these age categories, and partly by a need to have enough respondents in each group to yield stable estimates.

**RESULTS**

Forty-eight percent of the 224 physicians reported that his/her office's medical questionnaire, filled out on a patient's first visit, contained questions specific to the symptoms of PMS. The percentage ranged from 41% for female physicians who were less than 40 years of age to 50% for male physicians aged 40 years or older.

Ninety percent of the 67 physicians under the age of 40 years and 78%
Differences among preferred modes of treatment were observed according to the physician's age and sex, but were not substantial (Table 2). Part of those differences observed were attributable to an overall increase in the numbers of treatment approaches used by younger physicians as compared with older physicians.

DISCUSSION

The study results indicate that the major precipitating factor for PMS onset having the highest overall level of agreement was stress, which was scored by 63% of the study physicians. The most common mode of treatment for mild, moderate, and severe PMS was exercise, mentioned by 77, 72, and 57% of the study physicians, respectively.

The results of this study also indicate that substantial differences exist among obstetricians and/or gynecologists in their beliefs about PMS and in their preferred modes of treatment for women diagnosed as having PMS. In addition, some of these beliefs and preferred modes of treatment vary according to the physician's age and, particularly among young physicians, according to sex. Differences by age might result from beliefs or practices garnered from years of medical experience and/or proximity to medical school education.

It is interesting to note that nutritional approaches were mentioned as one of the leading modes of treatment for mild, moderate, and severe PMS (mentioned by 68, 58, and 48% of physicians, respectively), although the three components of diet queried as major precipitating factors for PMS onset were mentioned by only 17-25% of physicians. In addition, exercise was ranked as the leading preferred mode of treatment for mild, moderate, and severe PMS (mentioned by 77, 72, and 57% of the physicians, respectively), although lack of exercise was mentioned as a major precipitating factor for PMS onset by only 47% of physicians. Progesterone (suppositories or oral doses) was used by 45% of the physicians, although its effectiveness has been questioned.

Three possible sources of error warrant discussion. The first possible source of error pertains to our using a self-administered questionnaire to collect information about medical practices rather than using a more direct assessment of actual practice (reviewing medical records, for example). It is possible that some physicians reported practices that differ from their actual practices.

The second possible source of error pertains to limitations inherent in assessing "usual" medical care. Several physicians commented that their preferred modes of treatment for women with PMS depended on the specific PMS symptoms present rather than on an overall assessment of the severity of symptoms. For this reason, it may have been difficult for some physicians to report their "preferred" modes of treatment.

The third possible source of error is differences in the physicians' interpretations of the structured answers provided on the questionnaire. For example, "age-related," "depression," and "psychological difficulties," each listed as possible major precipitating factors for PMS onset, may have been interpreted differently by different physicians.

These possible sources of error notwithstanding, the results of this study document the considerable variability in beliefs about PMS onset and treatment approaches among obstetricians and gynecologists, and suggest the clear need for controlled trials evaluating the effectiveness of the various treatment modalities.
REFERENCES

Appendix B

Women’s Health Survey
WOMEN'S HEALTH SURVEY

GENERAL INFORMATION

1. What is your age? ________________ /__/__/ 4,5
2. What is your height? ________________ /__/__/ 6,7
3. What is your weight? ________________ /__/__/ 8-10
4. What is the reason for your visit? _______ /__/ 11

PREMENSTRUAL AND MENSTRUAL HEALTH

5. Do you experience premenstrual syndrome? No____ Yes___
(Premenstrual syndrome is an array of symptoms beginning approximately one week prior to each menstrual period and usually ending a couple of days prior to your period. Premenstrual syndrome is different from menstrual symptoms, which occur at the time of your period. Many of the most common symptoms of premenstrual syndrome are listed in question 6.)

6. If you do experience premenstrual syndrome, circle the severity of each the following symptoms you experience. (If you do not experience premenstrual symptoms on a regular basis each month, skip to question 11.)

   Depression ___ Mild Moderate Severe /__/ 13
   Tiredness ___ Mild Moderate Severe /__/ 14
   Irritability ___ Mild Moderate Severe /__/ 15
   Anxiety ___ Mild Moderate Severe /__/ 16
   Bloating and weight gain___ Mild Moderate Severe /__/ 17
   Headaches ___ Mild Moderate Severe /__/ 18
   Breast swelling, tenderness ___ Mild Mod Severe /__/ 19
   Craving for sweet foods ___ Mild Moderate Severe /__/ 20
   Craving for salty foods ___ Mild Moderate Severe /__/ 21
   Binge eating ___ Mild Moderate Severe /__/ 22
   Skin acne ___ Mild Moderate Severe /__/ 23
   Other (please specify) ______________ Mild Mod Sev /__/ 24
7. About how many days before your menstrual period do the premenstrual symptoms circled in question 6 occur? ________________  /__/ 25

8. Would you say that your premenstrual symptoms (described in question 6) overall are mild, moderate, or severe? ________________  /__/ 26

9. Are your premenstrual symptoms severe enough to cause you to miss work or interfere with your daily housework? No___ Yes___  /__/ 27

10. Are your premenstrual symptoms severe enough to cause you to take aspirin or other medications? No___ Yes___  /__/ 28

11. Does (did) your mother experience premenstrual syndrome? No___ Yes___ Unknown___  /__/ 29

12. Does your sister(s) experience premenstrual syndrome? No___ Yes___ Unknown___ No sisters___  /__/ 30

13. Circle the severity of the following menstrual symptoms which you regularly experience at the time of your period.

   Cramps ___ Mild Moderate Severe  /__/ 31
   Headache ___ Mild Moderate Severe  /__/ 32
   Tiredness ___ Mild Moderate Severe  /__/ 33
   Other (please specify) _____________ Mild Mod Sev  /__/ 34

   Do not experience discomfort or any of the above symptoms during menstrual period (skip to question 16) ______  /__/ 35

14. Would you say that your menstrual symptoms (described in question 12) overall are mild, moderate, or severe? ________________  /__/ 36

15. Are your menstrual symptoms severe enough to cause you to miss work or interfere with your daily housework? No___ Yes___  /__/ 37

16. Have you ever been told by a doctor that you have endometriosis? No___ Yes___  /__/ 38

17. Have you used oral contraceptives (birth control pills) within the past three months? No___ Yes___  /__/ 39
Please leave blank.

18. How many full-term pregnancies have you had? _____ /__/ 40

19. Which, if any, of the following procedures have you had?
   Tied tubes     Ovaries removed     None        /__/ 41
   Hysterectomy   Other (please specify)________

DIETARY HABITS

20. Are you taking any medications? Yes__ No__ If yes, list all medications you currently take, including any vitamins.__________________________ /__/ 42

21. About how many times during a typical day do you eat "sweets" or junk food? _________ /__/ 43

22. How many of the "sweets" or junk food consumed during a typical day (question 21) contain chocolate? _______ /__/ 44

23. About how many cups of each of the following beverages do you drink during a typical day? (One "cup" is equal to about eight ounces, or one measuring cupful.)
   Water __________   /__/ 45
   Fruit juice ________   /__/ 46
   Milk __________   /__/ 47
   Caffeine-free soft drink ________   /__/ 48
   Caffeine-containing soft drink ________   /__/ 49
   Hot chocolate ________   /__/ 50
   Decaffeinated coffee ________   /__/ 51
   Caffeine-containing coffee ________   /__/ 52
   Herbal tea (non-caffeine-containing tea) ________   /__/ 53
   Caffeine-containing tea ________   /__/ 54
   Milk shake, ice cream soda ________   /__/ 55
   Other beverages (note that alcoholic drinks are listed in question 24) ________   /__/ 56
24. About how many drinks of each of the following beverages do you consume during a typical week?

Beer (one can) __________  /__/ 57
Wine (six ounces)__________  /__/ 58
Hard liquor (one ounce)__________  /__/ 59

25. Would you be willing to be interviewed in person to provide more detailed information about your premenstrual and menstrual health, and about your dietary habits? No____ Yes____ If yes, please provide your name, address, and/or telephone number.

THANK YOU VERY MUCH FOR PARTICIPATING IN THE WOMEN'S HEALTH SURVEY