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Impact of Breast Cancer Treatments on Gonadal Function and Reproductive Health

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There is a growing body of epidemiological literature supporting the positive relationship between a woman’s endogenous lifetime hormone exposure and the risk of breast cancer. Specifically, early menarche and late menopause are associated with increased risk of breast cancer, and this risk is reduced by surgical oophorectomy in the premenopause. Breast cancer adjuvant treatments often lead to premature menopause, and this may be an important factor in the efficacy of these treatments in younger women. However, women who experience premature menopause are at increased risk of earlier cardiovascular disease, as well as premature osteoporosis. Further, numerous epidemiological studies support the benefits of supplemental estrogen therapy in the postmenopause as an effective means of reducing mortality from both cardiovascular disease and osteoporotic fractures. There is uncertainty about how all of these factors play out in breast cancer survivors who have experienced premenopausal disease. Therefore, the primary focus of this cross-sectional study is to examine gonadal function and reproductive health comprehensively in long-term survivors of breast cancer.
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Introduction

There is a growing body of epidemiological literature supporting the positive relationship between a woman's endogenous lifetime hormone exposure and the risk of breast cancer. Specifically, early menarche and late menopause are associated with increased risk of breast cancer, and this risk is reduced by surgical oophorectomy in the premenopause. Breast cancer adjuvant treatments often lead to premature menopause, and this may be an important factor in the efficacy of these treatments in younger women. However, women who experience premature menopause are at increased risk of earlier cardiovascular disease, as well as premature osteoporosis. Further, numerous epidemiological studies support the benefits of supplemental estrogen therapy in the postmenopause as an effective means of reducing mortality from both cardiovascular disease and osteoporotic fractures. There is uncertainty about how all of these factors play out in breast cancer survivors who have experienced premenopausal disease. Therefore, the primary focus of this cross-sectional study is to examine gonadal function and reproductive health comprehensively in long-term survivors of breast cancer.

Specific Aims

1. To recruit a sample of breast cancer survivors (BCS) who were 50 years or younger at diagnosis, and were treated initially at the Jonsson Comprehensive Cancer Center at UCLA between 1994 and 1997.

2. To recruit additional subjects with identical characteristics treated at Kaiser Permanente West Los Angeles or Kaiser Permanente Sunset between 1989 and 1997.

3. To survey these BCS to determine the effects of past treatment on menstrual history patterns and fertility, as well as past and current menopausal symptoms, and current health-related quality of life.

4. To measure current reproductive hormone status, cardiovascular lipid profiles, body composition and bone mineral density in these BCS to assess the late effects of breast cancer treatment on risk factors for coronary artery disease and osteoporotic fractures.

Description of Phases 1, 2, 3 and 4

The study is being conducted in four phases. In phase one, the UCLA Medical Center Tumor Registry and the Kaiser Permanente Tumor Registry are being used to identify a group of breast cancer survivors who were 50 years or younger at the time of diagnosis and who are currently disease free. Eligible breast cancer survivors are then invited to participate in study that will ask them to complete a survey questionnaire that reviews their menstrual and reproductive history, medication history (including past and current use of contraceptive and non-contraceptive hormones), pregnancy/fertility history, past and current symptoms that may be menopause related, use of alternative therapies, diet and physical activity levels, as well as standardized measures of health-related
quality of life. The survey also asks detailed information about each subject's cancer treatment, including type and duration of chemotherapy and hormone therapy received. In addition to analyzing the results from the survey, we will examine the medical and demographic characteristics of breast cancer survivors who participate in comparison with those who refuse.

In phase two of the research, all breast cancer survivors who completed the phase one survey questionnaire are invited to come to UCLA for an in-person visit to complete physical and laboratory studies. These include blood work for evaluation of cardiovascular lipids and gonadal hormones; measurement of blood pressure, height, weight and waist/hip girth; and performance of a bone mineral density test (BMD). The results of the questionnaire data and medical treatment details from phase one, as well as current gonadal hormone levels, will be used to explore the predictors of current health status/health-related quality of life, cardiovascular lipids, and bone mineral density. The analyses planned will examine whether a relationship exists between menstrual patterns after breast cancer and current health-related quality of life, lipid profiles, bone mineral density or body composition. These data will be useful in the management of women who are currently long-term survivors of breast cancer, and can be used to provide supporting pilot data for the design of a prospective longitudinal study examining the impact of breast cancer treatment on the long-term reproductive health of premenopausal women with breast cancer.

Since our original study was designed, we have added two new components - a study of neurocognitive functioning (phase three) and a longitudinal follow-up study of bone density (phase four). In phase three of the research, women who are between 2 and 5 years post-diagnosis who complete phases one and two and who meet other eligibility criteria will be invited to come to UCLA for an in-person visit to complete a battery of neurocognitive functioning tests. In addition to the neurocognitive tests, we will perform a single blood draw, as well as measure blood pressure and heart rate and collect saliva samples several times during the testing. The main analysis planned will examine whether a relationship exists between cognitive functioning and type of adjuvant therapy received (chemotherapy alone; tamoxifen alone; both chemotherapy and tamoxifen; or no therapy). The blood and saliva measurements are for examination of immune functioning and cortisol.

In phase four of the research, women who completed phase two approximately 18 months prior will be invited back to receive a follow-up bone mineral density. We have added this phase because of interesting preliminary findings from the cross-sectional evaluation in phase two. We plan to compare group data between the initial and the follow-up BMDs.
Progress report on second year of funding

Recruitment and Subject Characteristics

During the past year, we have continued to recruit long- and short-term survivors. Recruitment has gone very well, with the exception of a large number of invitation letters that came back as "return to sender." We pursued correct addresses for these women through current hospital databases and as a result, we have been able to make contact with a substantial number of these women.

Between October 1, 1999 and September 30, 2000, we sent invitation letters to 603 breast cancer survivors (184 short-term survivors identified by UCLA; 274 long-term survivors identified by Kaiser; and 145 short-term survivors identified by Kaiser) for phase one of the study. Among the 576 invitations that were not returned to sender, we have thus far received 407 responses (71%), and of those women, 309 (76%) were interested in receiving a screening call. Caucasian women expressed the most interest in hearing more about the study (80%), followed closely by Hispanic women and African American women (both 74%). Asian women were least likely to be interested in participating in the study (58%).

Between October 1, 1999 and September 30, 2000, 308 women have been screened for this phase of the study. Of those, 23 women were found to be ineligible, and 196 women successfully completed the questionnaire. Among the uncompleted questionnaires, 11 women refused after seeing the questionnaire, 53 women were closed out (they did not return their questionnaire within 60 days) and the remaining questionnaires are pending.

For phase two, we are approaching women who completed a questionnaire and who live in California to come in for an in-person visit, which includes a blood draw to measure cholesterol and hormone levels, and a DEXA scan to measure bone mineral density. Between October 1, 1999 and September 30, 2000, we mailed out 257 invitation letters for this second phase of the study. Of the 238 women whose invitation letters we have so far followed-up by phone, 55 (23%) were not interested in participating. Of the remaining women who were interested and eligible, 158 have completed the appointment. Among these women, 122 (77%) were post-menopausal, and 36 (23%) were pre-menopausal. All of the pre-menopausal women agreed to complete the menstrual diary calendars, in which a woman checks off her daily symptoms (bleeding, bloating, hot flashes, irritability, and joint aches) every day for a year, however 3 of these women subsequently changed their minds and did not fill out the calendars, and an additional 4 women became pregnant after agreeing.

We began inviting women for phase three in March 2000. As of September 30, 2000, we have invited 65 short-term survivors to come to UCLA for a battery of neurocognitive tests. Of these 65, 59 women have thus far responded to our invitation: 36 were interested in participating (61%) and the remainder were not interested. Of those
interested, 32 have been screened for eligibility; 7 were found ineligible (22%) and the remaining 25 were eligible and scheduled for an appointment. As of September 30, 2000, 22 women have completed this phase of the study.

Phase four was just initiated in September 2000, and as of September 30, we have invited the first batch of 11 women to participate. It is too early to determine interest in this phase of the study, but we anticipate it will be high.

Additional Data Collection

The recruitment numbers reported for phases one and two above contain only those subjects recruited with DOD funding for this particular study. However, this DOD funding was in fact used to expand on prior data already collected by a similar study that was initiated with NCI funding. Therefore, in addition to the data collected on the subjects described above, we have phase one data for an additional 173 long-term survivors (5-10 years since diagnosis), and biological data on 96 of these women. For all analyses, we will combine data from both the NCI and the DOD studies.

Reportable Outcomes

In June 2000, Dr. Ganz presented the first findings of our study at the DOD Era of Hope Meeting. The abstract and presentation were entitled, “Reproductive Health Effects of Breast Cancer Treatment.” Analyses for this presentation were based on findings from the first 376 completed questionnaires (which included data from this study combined with data from our similar NCI-funded study), as well as data from 189 bone density evaluations and biologic measurements. The main analysis for this presentation compared four different groups of survivors based on the adjuvant therapy they received for their breast cancer treatment. The four groups were: No therapy, chemotherapy alone, tamoxifen alone, and chemotherapy plus tamoxifen.

The results showed that there were very few differences between these groups. Specifically, there was no difference in quality of life measures (physical health, emotional health, energy/fatigue and general health), although fewer women in the “chemotherapy alone” group reported being sexually active compared to women in the other groups. Cardiovascular lipid profiles, blood pressure, weight and BMI did not differ according to treatment group, and neither did reproductive hormone levels, even after controlling for age and menopausal status. There did not appear to be a difference in the rate of bone fractures among the groups, however preliminary bone density findings suggested significantly diminished scores in long-term survivors who received chemotherapy alone.

Conclusion

As of September 30, 2000, we have questionnaire data on 482 long- and short-term breast cancer survivors. Additionally, we have biologic data and bone density
measurements on 261 (54%) of these women. During the next year of funding, we plan to invite the remaining 143 women on our tumor registry lists for phase one. Recruitment is going very well, and we anticipate being able to contact these remaining women by the end of 2000, after which we will begin the analysis and report-writing stage for this phase of the study.

We also plan to continue to invite geographically accessible women who complete phase one to come in for phase two (the bone density and biological measurement visit). We will also continue to recruit women for phases three and four of the study (the neurocognitive testing and the follow-up bone density visits).

In addition to ongoing data collection and beginning analyses on phase one data, our plans for the next year include drafting a manuscript that will look at the feasibility of recruiting breast cancer survivors from hospital tumor registries. In this paper we will report on the challenges and successes we encountered in recruiting the long-term sample from both a cancer center registry (UCLA) and a community hospital registry (Kaiser).