
SWAN: What It Is and What We Hope to Learn

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The ongoing Study of Women's Health Across the Nation will provide clinicians with a unique perspective on the menopause transition and associated changes, as experienced by a diverse, community-based population of women.

The Study of Women's Health Across the Nation (SWAN) is the first study to simultaneously evaluate multiple aspects of menopause-related changes in a multiracial/ethnic community-based sample of women. The study promises to provide unique data on the menopause experience and to give clinicians a broader, more balanced understanding of the changes that occur as women transition from pre- to postmenopause. The primary goals of SWAN are to describe the chronology of, and the normal variation in, the biologic and psychosocial characteristics of the menopause transition; to distinguish age-related changes from menopause-related changes; and to describe the health and risk factors after menopause, among community and/or population-based samples of women of various racial/ethnic backgrounds.

Background

Despite the fact that menopause is a universal event that will be experienced by approximately half the population living past midlife, there are many things we still do not know about this normal physiologic event. We know little about when physiologic changes begin to occur, how menopause is experienced by women of different racial/ethnic groups and what changes are related to menopause versus aging; these are just a few of the areas about which more knowledge is needed.

Several large, community-based studies of midlife women transitioning through menopause were begun in the 1980s and provided much-needed data on the epidemiology of menopause. Examples of some of these studies are the Massachusetts Women's Health Study, the Melbourne Women's Health Study and the Healthy Women Study. Some important lessons were learned from these studies that helped to shape the direction of subsequent research. The first of these lessons was the need to begin studying women earlier in the menopausal transition; findings from the studies mentioned above, most of which were initiated with

women at age 45 at baseline, demonstrated that perimenopause-related physiologic changes actually occur earlier than previously believed. We also learned that much of our knowledge about menopause had been based on research conducted largely with Caucasian women, making clear the need to learn more about the experiences of women of other races and ethnicities, especially in light of the increasing diversity in this country.

In the early 1990s, primarily at the impetus of the National Institute on Aging, a conference was organized under the auspices of the National Institutes of Health (NIH) to bring together experts to examine the "state of the art" of menopause. As a result of that meeting, the NIH issued a request for applications (RFA) to examine the physiologic and psychosocial changes that occur as women transition through the menopause. The RFA represented a major commitment of funds by the NIH, as well as the recognition of menopause as an important topic of research—and one about which relatively little was actually known. Once study sites were funded, the sites' investigators worked collaboratively to develop the protocol for what has become known as the Study of Women's Health Across the Nation (SWAN).

Goals and Characteristics

Funded primarily by the National Institute on Aging, with additional funding from the National Institute of Nursing Research, the Office of Research on Women's Health, the Center for Complementary and Alternative Medicine and the U.S. Department of Defense, SWAN is a prospective, multisite, multidisciplinary study of the natural history of menopause and the menopausal transition.

Several characteristics make SWAN's design unique; particularly, its focus on a community-based, multiethnic study population of younger women who are just beginning to experience changes associated with the menopausal transition. Very few menopause-related studies, especially those conducted in the United

States, have had the funding or ability to look at multiethnic/racial samples. (The very large Women's Health Initiative focuses exclusively on postmenopausal women.) As part of the SWAN design, each site recruited Caucasian women for approximately half of its sample, and a specific non-Caucasian group for the other half. SWAN includes non-Hispanic Caucasian (all seven sites), African-American (four sites), Chinese (one site), Hispanic (one site) and Japanese (one site) women.

SWAN's enrollment of a younger study population reflects the need for a shift in focus from changes that occur around the time of the final menstrual period, to those that begin earlier in the reproductive aging process. The women enrolled in SWAN's longitudinal (phase III) study ranged in age from 42 to 52 years at baseline and were pre- or early perimenopausal, enabling investigators to not only study women who are younger than those previously studied, but also to follow those women through the menopause.

Because the SWAN cohort was recruited from the communities in which the participating sites are located, rather than being patient-based, investigators have been able to learn not only about women who seek medical care related to the menopause, but also about those who do not. The community-based sample design also provides opportunities to examine factors such as those related to healthcare utilization and the use or non-use of hormone replacement therapy (HRT), ultimately providing clinicians with a more complete picture of the menopause experience and a benchmark for comparing their patients' experiences to those of the general population.

What sets SWAN apart from other studies even further is a design that enables investigators to prospectively study a diverse population of women in a single study. When multiple ethnic/racial groups are followed in a single study that employs the same measures and sampling techniques across the board, compari-

sons can be made that are extremely difficult when, for example, Hispanics are enrolled in one study and African-Americans are enrolled in another study that employs different measures and research designs.

Study Design

SWAN is being conducted under the auspices of a cooperative agreement between the NIH and seven study sites, as well as a data-coordinating center and two laboratory facilities (Table 1). SWAN consists of three phases: focus groups (phase I), a cross-sectional survey (phase II) and the longitudinal cohort study (phase III). Investigators have recently begun the fifth follow-up (annual) interviews of the longitudinal (phase III) portion of the study.

Phase I (focus groups). In September 1994, phase I of SWAN was initiated with 27 focus groups consisting of approximately 195 pre-, peri- and postmenopausal women from the study's target ethnic groups. The focus groups, which were carried out during the first year, were conducted in order to direct the study design and protocols, and to "ensure the relevance and the appropriateness of the protocols to the multiethnic cohort."¹ Specifically, the topics discussed in the focus groups were designed to ensure that the questions asked during phase III of the trial would be understood by, and relevant to the experiences of, women from the broad range of socio-cultural backgrounds to be targeted.

The focus groups were also intended to elicit discussions that would help investigators identify strategies to facilitate recruitment and retention among the various ethnic groups. In addition, the groups served as "testing grounds" for the menopause-related language to be used by the investigators; some focus groups were conducted for the sole purpose of determining the language used by the women to describe menopause and their views on this phase of life. This was done to ensure that terminology specific to the various cultures would not be overlooked or misunderstood, and that a Westernized view

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of menopause would not be imposed upon the participants in the cross-sectional and longitudinal studies.

Phase II (cross-sectional study). The cross-sectional survey had two main purposes: One was to identify and recruit eligible women into the longitudinal cohort, and the other was to provide a "snapshot" of women at midlife that included their health, lifestyles, symptoms, age at natural menopause and prevalence of surgical menopause. Fifteen-minute interviews (primarily by telephone) were conducted with more than 16,000 women, ages 40-55, from all five of the target ethnic groups: Caucasians (7,772, 48.5%), African-Americans (4,383, 27.4%), Hispanics (including Mexican) (1,955, 12.2%), Japanese (854, 5.3%) and Chinese (651, 4.1%).

Interviews also were conducted with women who identified themselves as belonging partly, but not primarily, to one of the target ethnic groups (including "mixed" [44, 0.3%] and "other" [357, 2.2%]). These interviews provided us with cross-sectional data not only on women who would be entering the cohort (pre- or very early perimenopausal), but also on surgically menopausal women, on those already well into the transition and on postmenopausal women.

Among the published findings from the cross-sectional data are the following:

- Surgical menopause was most common among African-American women and least common among Japanese and Chinese women.²
- Some degree of racial/ethnic differences was noted with respect to a number of variables examined (age at menopause, reported symptoms, surgical menopause, attitudes toward menopause, body mass index), even after controlling for differences in socioeconomic status and lifestyle

<ul style="list-style-type: none"> • Predictors of hysterectomy • Health status and functional limitations • Prevalence of urinary incontinence • Predictors of physical activity • Self-defined menopause status • Attitudes toward menopause • Quality of life • Correlates of psychological symptoms • Symptom reporting • Hormone use

factors such as smoking and level of education.²⁻⁶

- Most physical symptoms were reported less frequently by Japanese and Chinese women, while vasomotor symptoms were reported more frequently by African-Americans, after controlling for menopausal status, age, smoking, body mass index, socioeconomic status and physical activity.³
- Most physical symptoms were reported more frequently by women who reported difficulty paying for basics, by women who smoked and by those who reported engaging in less physical activity than other women of their age.³

Authors of other published cross-sectional articles and papers currently in progress are looking at correlates of hysterectomy, health status and functional limitations, predictors of physical activity, quality of life and hormone use (Table 2).

Phase III (longitudinal cohort study). The longitudinal cohort study is the major focus of SWAN and addresses the primary research questions.

A total of 3,302 women (approximately 450 at each of the seven sites) from the cross-sectional sample were enrolled in the longitudinal cohort study. The women ranged in age from 42 to 52 years at baseline, reported having menses within the previous 3 months, had an intact uterus and at least one ovary, and were not taking exogenous reproductive hormones. An extensive battery of examinations was undertaken with each woman at baseline (requiring approximately 5 hours to complete the entire protocol), and participants have returned for 2-hour visits at each of four annual follow-ups. In addition to the measures described below, annual follow-up visits include surveys on a broad range of topics, such as healthcare utilization, symptoms, general health, attitudes toward menopause and menopause status.

Areas of Study

The focus in SWAN is on changes in risk

as women transition through the menopause, rather than on specific disease endpoints, such as osteoporosis or cardiovascular disease, for which much longer-term follow-up would be required. While the study does involve determining whether racial/ethnic differences exist with respect to women's menopause experiences, one of its primary goals is to go a step further and learn why those differences exist and what factors might help to explain them. The areas of study in SWAN's longitudinal cohort are described below.

Bone density and body composition. Lumbar spine, hip and whole-body bone mineral density (BMD) measurements are obtained annually at five study sites in all target ethnic groups, with the exception of Hispanic women. Serum and urinary markers of bone turnover (formation and degradation) were assessed at baseline and at the first two annual follow-up visits in order to assess factors such as the way in which markers of bone turnover predict subsequent bone loss. In this way, BMD measurement provides a picture of bone composition at a given point in time, and turnover markers provide an indication of how quickly any remodeling is taking place. Body composition (lean and fat mass) and its changes during the menopausal transition are also assessed annually in these same study participants.

Cardiovascular measures/risk factors. Annual cardiovascular measures are obtained at all seven study sites, in all ethnic groups, and include blood pressure and adiposity (waist, hip, height and weight, for computation of body mass index). Serum is collected annually, and cardiovascular data, including those on lipids, lipoproteins, glucose, insulin and clotting factors, are measured every other year. Serum samples from the intervening years are being stored for future analyses. At one center, carotid ultrasonography is being conducted. Cardiovascular measures are assessed for change over the menopause and for any variance by ethnicity.

Ovarian markers. In addition to stan-

dard measures, such as follicle-stimulating hormone (FSH) and estradiol, other markers of ovarian aging being assessed are inhibin-B (starting with the fourth annual follow-up) and estrone (postmenopausal women only, starting with the fourth annual follow-up). Additional hormones being measured include dehydroepiandrosterone sulfate, sex-hormone-binding globulin and testosterone. All of these hormones are measured annually in all ethnic groups. Thyroid-stimulating hormone was measured at baseline and at the fourth annual follow-up.

Menstrual status. Questions intended to determine menopausal status, such as those related to menstrual periods, surgeries (e.g., hysterectomy and oophorectomy) and use of HRT, are asked during the annual interviews. In addition, study participants keep monthly menstrual calendars to document bleeding patterns.

Symptoms. Symptoms commonly associated with menopause and aging, such as hot flashes, night sweats, mood changes, fatigue and lack of energy, are assessed annually via survey at all seven sites, in all ethnic groups. Several symptoms are also measured on the monthly calendars.

Psychosocial factors. At each annual visit participants are surveyed about psychosocial issues, such as quality of life, depression, stress, social support and life events. Information pertaining to sexual function is obtained via self-administered confidential questionnaire.

Epidemiologic issues. Factors related to healthcare utilization, initiation and discontinuation of HRT, smoking, physical exercise, etc., are assessed annually during follow-up interviews. Information pertaining to diet was obtained at baseline and at the 5-year follow-up visit, since dietary habits are known to change more slowly than are the variables being assessed annually.

Implications for Practice

One of the goals of SWAN is to relate hormonal and bleeding characteristics to changes in factors such as BMD, cardio-

vascular status, carbohydrate metabolism, etc., and to determine how these factors relate to one another. In other words, it is anticipated that the findings from the longitudinal study will allow us to determine, for example, how much of the cardiovascular changes that occur in midlife women is related to menopause, versus age, diet and other nonhormonal factors. We should also be able to relate psychosocial and behavioral changes to physiologic changes, to see if and how they are associated and to tease out the effects of menopause from those of age and behavioral change.

Findings from these analyses will allow clinicians to more accurately determine the cause of symptoms that occur around the time of menopause—rather than assuming that those symptoms must be related to hormonal changes—and to counsel patients more effectively. Weight gain serves as an example of an occurrence that many women attribute to menopause, *per se*. Recent findings, however, demonstrated that behavior and physical activity actually contributed to weight and weight gain during midlife to a greater degree than did menopause status, in studies that included pre-, peri- and postmenopausal women.^{5,7,8}

Change in sexual functioning is another example of an occurrence that is frequently attributed to menopause, but could actually be related to other factors (e.g., age, other life events, or health changes in aging partners). Said differently, the SWAN data will make clinicians (and patients) aware of a range of possibilities to be explored when looking for the cause of symptoms experienced during the menopause transition. The findings will also have implications for the HRT decision-making process, as we attempt to make distinctions between what can be attributed to menopause-related hormonal changes and other factors.

The SWAN data will also provide clinicians and their patients with a reference for “normal” occurrences, such as those related to bleeding patterns. For example, the knowledge that a particular bleeding

pattern is normal and transient at a specific age, during a particular stage of the menopausal transition, could avert the need for invasive procedures that might be undertaken without such knowledge.

The findings with respect to differences between the menopause experiences of women from different sociocultural backgrounds promise to offer new and exciting insights with the potential to optimize individualized patient care. This benefit notwithstanding, any information about differences among ethnic groups needs to be handled with the utmost vigilance, to prevent overgeneralization. This is especially true of research findings pertaining to sensitive areas, such as sexual functioning and cognition.

Limitations. Ideally, all five of the ethnic groups being studied in SWAN would be represented at each of the seven study sites; investigators could then control for cultural and/or environmental factors associated with geographic location when making ethnic comparisons. This limitation, which “comes with the territory” in this type of multisite study design, is of particular concern for the three ethnic groups that are represented in only one site each (Japanese, Hispanic and Chinese women). Assessment of site-to-site variability within each of these three ethnic groups is not possible; however, data from Caucasian women—who are being studied at all seven sites—are useful in estimating site differences within ethnicity, which helps to distinguish the roles of ethnicity from those of geographic area.

Present Status

SWAN is currently funded for five annual follow-ups (six visits, including baseline), the last of which was recently begun; several more years of follow-up are now being considered.

A number of articles presenting data from the cross-sectional phase of SWAN have been published or are ready for publication. These cross-sectional survey papers address a range of topics, including predictors of hysterectomy,

prevalence of urinary incontinence, hormone use, quality of life, correlates of psychological symptoms and attitudes toward menopause. Baseline articles detailing results from the cohort study will follow shortly thereafter. In the meantime, a Web site intended to provide the public with updates on SWAN is now in the planning stages. ■

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Daily Hormone Study

The Daily Hormone Study, a substudy of SWAN initiated at the first annual follow-up, promises to provide a unique perspective on hormonal changes and their effects on bleeding patterns and symptoms experienced during the menopausal transition. The substudy involves approximately 900 women across all seven sites and from all five of SWAN's target ethnic groups.

At each annual follow-up visit, Daily Hormone Study participants are asked to collect daily urine samples (first morning void) for either an entire menstrual cycle or, for those who don't have another period within 50 days, for 50 days. The samples are analyzed for reproductive hormones, including luteinizing hormone (LH), estrogen, progesterone and follicle-stimulating hormone (FSH). The profiles are examined cross-sectionally at each annual visit, to assess the variation from woman to woman across the substudy population. Longitudinal analyses are done to see how the individual women's hormonal profiles for each menstrual cycle or 50-day duration change over time in conjunction with more overt signs of the menopausal transition, such as changes in bleeding patterns. (The women taking part in the Daily Hormone Study also provide urine/serum samples for the annual assessments of hormonal profiles conducted with all SWAN participants.)

The women in the substudy are also asked to keep daily diaries to document a relatively small number of symptoms, such as irritability, vasomotor symptoms (hot flashes and night sweats), headache and changes in libido. These symptoms are then assessed in conjunction with the daily measures of hormones.

Factors such as hormone levels, menopause status and mood have typically been followed on an annual basis, providing an extremely gross measure with which to evaluate change. Because changes occur so rapidly during the perimenopause, annual assessments do not provide accurate depictions of the changes experienced by the individual woman on a daily basis over the course of her menstrual cycle, and their association with changes in mood, vasomotor symptoms, and so on. Daily measures ensure that day-to-day hormonal changes, such as the LH surge or the peak in FSH, will not be missed. Capturing daily changes is especially important as periods become irregular and fluctuations in hormone levels might become stronger and more rapid.

Findings from the Daily Hormone Study will provide a much more precise picture of what actually occurs during the menopausal transition, and will allow us to answer some questions with important implications for clinical practice. For example, hysterectomy is often used to control "abnormal" menstrual bleeding in women in their 40s and 50s. Many symptoms, such as excessive bleeding, are amenable to short-term medical management and will disappear with the transition to postmenopause. The Daily Hormone Study will help identify hormonal patterns occurring in women with dysfunctional bleeding who might be candidates for nonsurgical treatment.

Another example involves daily changes in mood or vasomotor symptoms documented by the substudy participants. Are these changes associated with hormones? If so, what type of relationship exists? Is it absolute levels of hormones, or the changes in these hormones, that are most important? These are the types of questions we hope to answer.

Other substudies with the SWAN longitudinal cohort are being conducted as site-specific studies. In one such study, carotid ultrasonography is being used to assess variables such as vessel elasticity. Another single-site study involves short-term memory testing, to assess whether any cognitive changes are associated with menopause—something that has not before been carried out prospectively in a naturally menopausal sample.

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