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The SWAN Song: Study of Women's Health Across the Nation's Recurring Themes

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SYNOPSIS

There is a belief that reproductive health is a reflection of whole-body health. It then follows that abnormalities of reproductive milestones may be a manifestation of aberrant or unhealthy aging. In order to assess how menopause per se and the process of the menopause transition may affect future health risks and outcomes, the Study of Women's Health Across the Nation was begun in 1994. SWAN, now in its 14th follow-up year, has characterized the life experience of a multi-ethnic cohort of mid-life US women in an unprecedented level of detail. Several enduring themes have emerged from SWAN that have associated certain patterns of hormones and symptoms with metabolic status. Moreover, the nature of relationships between hormones, body size, ethnicity, metabolic status and cardiovascular disease symptoms risk vary as women traverse the menopause and ovarian hormone production eventually ceases. This review will describe these cross-cutting themes and their possible meaning for the health of the mid-life woman.

Keywords

Menopause; menopause transition; metabolic syndrome; hot flashes; estrogen; progesterone

Introduction

Menopause transects the aging process in women and presents an immediate dilemma for health care providers, who are often prevailed upon to determine whether or not a specific symptom or problem is attributable to the ovarian hormonal changes associated with menopause or simply to the aging process. While the former is sometimes treatable with hormone therapy or other non-hormonal remedy that addresses the lack of ovarian function,

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the latter problems are often irreversible and only addressed by strategies designed to treat or delay the development of a chronic condition. It is therefore important for clinicians to have as clear as possible a categorization of the menopausal process and attribution of symptoms. In addition, the development of chronic diseases of aging should be predicted and addressed in mid-life women. This preface will discuss the overall impact of menopause and the menopausal transition on women's health, and will identify the impacts of common modifiable (obesity, lifestyle) and non-modifiable (ethnicity) conditions upon the process of menopause and subsequent health and risks for disease, principally cardiovascular disease.

Does Age at Menopause Influence the Lifespan?

It is tempting to speculate that reproductive health is a reflection of overall health. If so, it follows that women with early menopause are likely to be less healthy and women with late menopause are more likely to be healthy. While there are limited data to support this concept, it is at best an oversimplification. Cooper, et al, using data from the National Health and Nutrition Examination Study (NHANES), observed an increased adjusted mortality rate ratio of 1.50 (95% CI, 0.97–2.34) for women with a natural menopause at age < 40, with an increased risk of cancer-related mortality (adjusted rate ratio of 2.34, 95% CI, 1.20–4.58)⁴. Data from the Women's Ischemia Syndrome Evaluation indicates that hypogonadotropic, hypoestrogenic amenorrhea prior to the age of natural menopause is strongly related to cardiovascular disease risk (OR 7.4; 95% CI: 1.7–33.3)¹. Another recent evaluation of 2,509 women from the Multi-Ethnic Study of Atherosclerosis (MESA) observed an association between early menopause (age 45 or younger) and cardiovascular disease, stroke and CHD death³¹.

The above studies have been based upon association, and cannot determine causality. Data from the Framingham study of cardiovascular risk implies that the widely accepted causal inference that loss of estrogen due to menopause results in increased heart disease may be incorrect, or is at least an oversimplification. These investigators studied 695 women who were premenopausal at the onset of the Framingham study and who underwent menopause during follow-up. They found that each *premenopausal* 1% increase in Framingham score was associated with a decrease in menopausal age of 1.8 years¹⁶. Thus, it is possible that adverse cardiovascular risk predisposes women to earlier loss of ovarian function.

Ethnicity is also related to timing of menopause and the risk for surgical menopause. African-American women are more likely to undergo hysterectomy and surgical menopause²³, whereas Hispanic women are more likely to undergo early or premature natural menopause¹⁸.

If early menopause predicts early mortality, then it may follow that late menopause predicts longevity. In one study that has examined this question, the life expectancy for a woman who underwent menopause at age 55 was two years longer than a woman who underwent menopause at age 40²¹. Women who underwent later menopause appeared to be at higher risk of breast and endometrial cancer but overall lower risk of CHD. This observation implies that a prolonged reproductive life span results risks that must be balanced against the acquired (or pre-existing) risks that predispose a woman to earlier menopause. Thus, there may be an optimal window for menopause that balances these two competing risks. It is interesting that despite dramatic increases in overall health and longevity in industrialized populations over the past century, there has only been a small delay in the age at menopause. Taken together, the data imply that age at menopause is not a major predictor of the life span.

In contrast to women who have undergone natural menopause, women with surgical removal of their ovaries appear to suffer increased morbidity from a number of causes. An

ongoing cohort study of over 1,000 women who underwent premenopausal bilateral oophorectomy, 1,200 who underwent unilateral oophorectomy, and 2,400 controls has indicated increased CHF, stroke, fracture, Parkinsonism, cognitive impairment and dementia, and depression and anxiety²². Interestingly, when mortality was examined within this cohort, the only group that appeared to have significantly increased mortality was women who underwent prophylactic bilateral oophorectomy prior to age 45²⁵. Use of hormone therapy did not uniformly prevent subsequent morbidities.

A Brief Description of SWAN

The Study of Women's Health Across the Nation (SWAN) is a multi-center, multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. A total of 3,302 women were enrolled at seven clinical sites between 1996–1997. At the time of enrollment, women were premenopausal, not taking hormones and between 42–52 years of age. Participants self-identified as African-American (28%), Caucasian (47%), Chinese (8%), Hispanic (8%), or Japanese (9%). Women were followed annually for ten years and are now being followed every other year with the year 14 visit set to begin in the fall of 2011.

SWAN has a multi-disciplinary focus and thus has repeated measures of bone health, cardiovascular risk factors, psychosocial factors, and ovarian hormones. Thus, SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in a community based sample. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period and we are focusing on outcomes such as fractures, depression, subclinical cardiovascular disease, cardiovascular events and physical and cognitive function.

SWAN Theme: Ethnicity is related to many outcomes

The SWAN cohort includes Caucasian women at all sites, African-American women at 4 sites, and non-Mexican Hispanics, Chinese-Americans and Japanese-Americans each from a single site. Because ethnic minority groups were not recruited from all sites, there is the potential for site-to-site variation that can influence risks and outcomes. Indeed, SWAN outcomes vary by site as well as by ethnicity. Site variation is even observed among the Caucasian and African-American groups. SWAN data are therefore often presented with statistical adjustments for these site and ethnic associations.

African-American women are more likely to report heavy menstrual bleeding and to undergo hysterectomy²³. Hispanic women are more likely to develop metabolic syndrome and incident type 2 diabetes mellitus. When bone density is examined as a function of ethnicity, and statistical adjustments are made for BMI, non-Hispanic Caucasian women have been found to have the lowest bone density in the cohort⁷. These key findings of SWAN will be presented along with each contribution to this issue.

There are also several nuances *within* the ethnic groups in SWAN. The Hispanic subgroup, for example, is a mixture of Central/South American, Cuban, Puerto Rican and Dominican women. Within the group of Hispanic women, there is also evidence of variation. Puerto Rican women had the highest rate of metabolic syndrome, anxiety and depression^{5,12} and trouble sleeping¹¹ compared to other Hispanic women, whereas Central American women reported more frequent vasomotor symptoms than other subgroups¹¹. This was despite the fact that the Puerto Rican participants in SWAN were more likely to report higher acculturation¹².

A second complication arises when there is little or no overlap between traits found in different ethnic groups. BMI is such an example. African American women have the highest mean BMI in SWAN, and in the highest BMI categories, there are few to no Chinese and/or Japanese Americans. Yet BMI clearly modifies several key SWAN-related outcomes. Among these are hot flashes. African-American and Hispanic women are the two highest BMI groups in SWAN and reported more frequent and severe hot flashes than other ethnic groups at baseline¹⁰. Separating the ethnic contribution from the BMI associated contribution to hot flashes becomes challenging when the between group differences are large.

SWAN Theme: Socio-economic Status (SES) is Related to Many Outcomes

A second theme that has emerged from SWAN is that relative economic well-being, education, and financial security (or lack thereof) are related to outcomes and risks. SWAN utilizes several methods for determining SES. Educational level is one variable. Economic strain is assessed a question that addresses the degree of difficulty the participant experiences in paying for the basic necessities of life (food, clothing, shelter)?” Adverse life events are also assessed. Primary outcomes of SWAN are related to SES. Women of low SES are more likely to experience early menopause^{19,27}. Factors associated with low SES (financial strain, adverse life events, poor social support) are also related to increased depressive symptoms² and to menopausal symptoms⁸.

Women of lower socioeconomic status who are not within the SWAN cohort are more likely to experience early menopause, and appear to have more and worse symptoms. This is consistent with other studies that have evaluated the effects of SES on the menopause transition. In a cohort study of perimenopausal women in the Bronx, half of whom were HIV infected and half of whom used street drugs, the median age at menopause was found to be 46–47 years, substantially lower than 51.4 years, the median age at the FMP in SWAN^{9,27}. Thus, the menopausal experience is likely to be more difficult for women in vulnerable groups.

SWAN Theme: BMI Is Associated With Hormone Levels and Study Outcomes

Weight gain has long been observed to occur in conjunction with the menopausal transition, but studies prior to SWAN have concluded that weight gain is driven primarily by age. SWAN has been able to identify specific aspects of the transition that contribute to weight gain over and above age. We have found that higher androgens, lower SHBG, surgical menopause and early hormone therapy use are all key factors associated with the development of obesity and/or severe obesity. Results also underscore the importance of physical activity as a preventive strategy for weight gain²⁹.

The link between body weight and hormone levels is another interesting phenomenon that SWAN has been able to shed light on. The median adjusted BMI of the women in SWAN was 27.3 kg/m² at the study baseline visit²⁶. Higher BMI is associated with worse vasomotor symptoms as women traverse the menopause¹³, but this relationship may change once women become postmenopausal¹⁴. High BMI is also related to the trajectory of reproductive hormones across the transition. Women of high BMI have lower gonadotropins and estradiol prior to menopause, and have a lesser decline in estradiol associated with the transition²⁴. BMI is related to mood, symptoms and hormones as well as metabolic syndrome and cardiovascular risk factors in SWAN.

The relationship of BMI and several key SWAN outcomes appears to change as women complete the transition into menopause. This is explainable by the fact that adipose tissue causes increased peripheral estrogen production from hormone precursors. When the ovary is still producing estrogen, prior to menopause, the contribution of adiposity to the total body estrogen pool is minimal. However, once the ovary becomes essentially inactive after menopause, the adipose contribution to the total body estrogen pool becomes biologically significant. This may account for the greater risk of vasomotor symptoms in obese women prior to menopause (due perhaps to increased insulation of the body by fat), and a loss of this relationship after menopause (due to a contribution of peripheral conversion to estrogens by adipose tissue).

Metabolic syndrome (MS) was present in almost 14% of the women in SWAN by the time of the final menstrual period.¹⁵ Incident metabolic syndrome is predicted by stage of perimenopause, androgens, and the testosterone to estradiol ratio—an index of relative androgen excess.^{15,30} After menopause, the risk of developing metabolic syndrome appears to decrease. There thus appears to be a contribution of menopause apart from aging per se on the development of MS.

Theme: The Late Peri-menopause as a critical time when the biological effects of the transition are consistently observed

One of the most consistent findings across SWAN has been that late perimenopause (three months of amenorrhea) appears to be the time frame that coincides most strongly with both symptoms and measureable physiological changes across all health areas. Transition to late perimenopause was the strongest predictor of vasomotor symptoms¹⁰. From a bone health perspective, SWAN has shown that bone loss accelerates substantially in the late perimenopause to an average loss of 0.018g/cm²/year in the spine and 0.010 g/cm²/year in the hip⁶. From a psychosocial perspective, women with a low CES-D at baseline had significantly higher odds of depressive symptoms when they reached the late perimenopause³. In addition, in an evaluation of depression and inflammatory markers, late perimenopausal women had elevated Factor VIII, fibrinogen and tPA-ag levels, suggesting that the late perimenopause may be uniquely associated with alterations in hemostasis²⁰. The prevalence of sleep difficulty was also found to be highest in the late perimenopausal stage. Most importantly, this finding was independent of the effects of vasomotor symptoms¹⁷. Finally, from a cardiovascular perspective, late peri and postmenopausal women were found to have larger common carotid artery lumen and adventitial diameters than pre and early perimenopausal women. This suggests that declining estrogen levels are associated with remodeling or adaptation of the vasculature³².

Summary

The SWAN Study has provided a tremendous amount of insight into the many determinants and interactions that predict health and wellness as well as disease risk in midlife women. Major factors that influence risk include race/ethnicity, SES and adverse life events, and BMI—particularly metabolically unhealthy obesity. As most of the cohort has now completed the transition into menopause, we anticipate that there will be changes in the risk factors for disease and will be able to track health outcomes in greater numbers.

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Figure 1. SWAN Cohort Assembly. A cross-sectional survey of 16,065 women was conducted, from which most sites drew their samples for the longitudinal study (3,302 women at baseline). The various substudies within SWAN are listed in this figure, with their initial sample sizes. Details of the SWAN cohort assembly and design are available through reference²⁸.