

Changes in Cardiovascular Risk Factors by Hysterectomy Status With and Without Oophorectomy

Study of Women's Health Across the Nation

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- Objectives** The aim of this study was to compare the changes in risk factors for cardiovascular disease (CVD) leading up to and after hysterectomy with or without bilateral oophorectomy with the changes observed up to and after natural menopause.
- Background** Evidence suggests that hysterectomy status with or without bilateral oophorectomy might increase risk for CVD, but most studies retrospectively assess menopausal status.
- Methods** Study of Women's Health across the Nation enrolled 3,302 pre-menopausal women not using hormone therapy between 42 and 52 years of age and followed them annually for over 11 years for sociodemographic characteristics, menopausal status, surgeries, body mass index, medication use, lifestyle factors, lipids, blood pressure, insulin resistance, and hemostatic and inflammatory factors. By 2008, 1,769 women had reached natural menopause, 77 women had a hysterectomy with ovarian conservation, and 106 women had a hysterectomy with bilateral oophorectomy. Piece-wise hierarchical growth models compared these groups on annual changes in CVD risk factors before and after final menstrual period or surgery.
- Results** Multivariable analyses showed that annual changes in CVD risk factors did not vary by group, with few exceptions, and the significant group differences that did emerge were not in the anticipated direction.
- Conclusions** Hysterectomy with or without ovarian conservation is not a key determinant of CVD risk factor status either before or after elective surgery in midlife. These results should provide reassurance to women and their clinicians that hysterectomy in midlife is unlikely to accelerate the CVD risk of women. (J Am Coll Cardiol 2013;62:191–200)
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Elective hysterectomy is a common surgical procedure to improve quality of life among symptomatic women approaching menopause (1–3). The clear benefits of surgery for reducing debilitating symptoms must be considered in light of potential long-term health consequences, including

cardiovascular disease (CVD). The cardiovascular risk associated with hysterectomy, especially accompanied by bilateral oophorectomy, is not yet clear. In the Framingham Heart Study, women who had a hysterectomy, especially with bilateral oophorectomy, were later at elevated risk for CVD, adjusting for age group and smoking status (4). In the Nurse's Health Study, women who had a bilateral oophorectomy, usually occurring in the fifth decade, were at greater risk for incident coronary heart disease and total mortality than women who had a hysterectomy without oophorectomy (5). By contrast, in a large registry of Swedish women, the risk for incident coronary heart disease, stroke, and heart failure during the follow-up was not confined to women with hysterectomy accompanied by bilateral oophorectomy; both surgical groups were at elevated risk (6). However, this relationship was only observed among women 50 years of age or less, and smoking was not statistically controlled. In an older cohort of women enrolled in the Women's Health Initiative, women with bilateral oophorectomy and

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**Abbreviations
 and Acronyms**

- Apo** = apolipoprotein
- BMI** = body mass index
- CRP** = C-reactive protein
- CVD** = cardiovascular disease
- FMP** = final menstrual period
- HDL-C** = high-density lipoprotein cholesterol
- HOMA-IR** = homeostasis model of assessment–insulin resistance
- HT** = hormone therapy
- LDL-C** = low-density lipoprotein cholesterol
- PAI** = plasminogen activator inhibitor
- SBP** = systolic blood pressure
- tPA-ag** = tissue plasminogen activator antigen

hysterectomy did not have a greater incidence of CVD, adjusting for a large number of CVD risk factors (7), compared with women with hysterectomy alone—similar to the results from the Swedish registry. In the same study, women who had hysterectomy regardless of ovarian conservation had elevated levels of CVD risk factors and were more often diabetic and hypertensive (8), compared with postmenopausal women who had not had a hysterectomy. Furthermore, hysterectomy, regardless of ovarian conservation, was associated with incident CVD, with associations largely attenuated after introducing a wide array of cardiovascular risk factors and sociodemographic characteristics.

Taken together, the findings raise a number of important issues. Because these studies only assessed CVD risk factors years after hysterectomy and/or oophorectomy, without assessment of pre-surgery CVD risk-factor levels, it is unknown whether elevated CVD risk led to the conditions warranting a surgical menopause or whether CVD risk was accelerated post-surgery. For example, obesity in pre-menopausal women increases the likelihood of abnormal bleeding and fibroids, which are common indications for these gynecologic surgeries (9–12). It is also not clear whether hysterectomy with versus without ovarian conservation has similar or different effects on CVD risk factors, compared with not having surgery and experiencing a natural menopause.

One approach to addressing these issues is to describe the prospective changes in cardiovascular risk factors before and after elective hysterectomy with or without bilateral oophorectomy in relation to changes in CVD risk factors that occurred in a comparable period of time before and after final menstrual period (FMP) in women who experienced a natural menopause. This report is based on cardiovascular risk factor data from SWAN (Study of Women’s Health across the Nation), a study of a multiethnic sample of women early in the menopausal transition who were subsequently followed annually. In a prior SWAN report, we found that the time interval around FMP due to natural menopause was associated with substantial increases in low-density lipoprotein cholesterol (LDL-C) and apolipoprotein (Apo) B (13). We address in this report whether even larger increases in lipids and other risk factors—including blood pressure, insulin resistance, and hemostatic factors—occur in women who had a hysterectomy with or without bilateral oophorectomy compared those who had a natural menopause. We also

examined these patterns with and without consideration of obesity, given that body mass index (BMI) increased after bilateral oophorectomy relative to natural menopause in the present sample (14).

Methods

Participants. SWAN is a multi-site community-based prospective study designed to examine the physical and psychological health of women as they undergo the menopausal transition. Details of the SWAN design and recruitment procedures have been reported elsewhere (15). At baseline, all SWAN participants had an intact uterus and at least 1 ovary and met the additional eligibility criteria: 42 to 52 years of age, not pregnant, not using reproductive hormones, and having 1 or more menstrual cycles in the 3 months before the interview. Each site recruited non-Hispanic Caucasian women as well as women belonging to a pre-determined racial/ethnic minority group: African-American women in Pittsburgh, Pennsylvania; Boston, Massachusetts; Detroit, Michigan; and Chicago, Illinois; Japanese women in Los Angeles, California; Hispanic women in Newark, New Jersey; and Chinese women in the Oakland area of California. Participants were recruited with established sampling techniques, random digit dialing, and random sampling from lists of names or household addresses. Select sites supplemented primary sampling frames to obtain adequate numbers of racial/ethnic minority women. Seventy-three percent of the women selected were contacted and provided information to determine eligibility; 51% (n = 3,302) of eligible women enrolled.

Participants returned to their local site facility annually for interviewer- and self-administered questionnaires, a fasting blood draw, and assessments of physical measures. Data collection for this analysis spanned from 1996 to 2008. SWAN was approved by the institutional review boards at each site, and each participant provided written, informed consent. Data collection ceased at the New Jersey SWAN site after 2001 for reasons unrelated to scientific aspects of the project. Because this resulted in an average length of follow-up for this site being systematically shorter than that of any other site, data from this site were excluded from the current analysis.

Measures and procedures. **MENOPAUSAL AND HYSTERECTOMY STATUS.** Menopausal status and the occurrence of hysterectomy and/or oophorectomy were assessed annually in SWAN. Participants were asked whether they had a “hysterectomy (an operation to remove your uterus or womb)” and whether they had 1 or both ovaries removed since the last study visit. Those who indicated hysterectomy were further divided into those with and without bilateral oophorectomy, provided their hysterectomy occurred before becoming naturally post-menopausal. Medical records were sought for all women who reported hysterectomy; of the 166 obtained, all but 1 confirmed hysterectomy and/or oophorectomy. Women were categorized as naturally post-menopausal if

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