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The Effect of Prior Oophorectomy on Changes in Bone Mineral Density and Carotid Artery Intima-Media Thickness in Postmenopausal Women

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Abstract

Objective—To determine the effect of prior oophorectomy in healthy postmenopausal women on the rate of loss of bone mineral density (BMD) and rate of increase in carotid artery intima-media thickness (CIMT)

Design—Secondary analysis from a randomized controlled trial

Setting—University-based research clinic

Patient(s)—222 healthy postmenopausal women in the Greater Los Angeles Area

Intervention(s)—Baseline and annual screening of BMD and assessment of CIMT every 6 months for a total of 3 years

Main Outcome and Measure(s)—Changes in BMD and CIMT during postmenopausal years

Result(s)—Among women who were menopausal more than 10 years, the rate of CIMT progression was statistically significantly less in women with intact ovaries compared to prior oophorectomy. In women 5-10 years postmenopausal, there was a trend toward a slower loss of BMD in those who retained their ovaries and in women more than 10 years menopausal there was significantly less BMD loss in those who retained their ovaries.

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Conclusion(s)—As time from menopausal transition increases, retained ovaries are associated with a slower rate of bone loss and a slower rate of thickening of the carotid artery wall compared to rates in menopausal women with oophorectomy.

Keywords

menopause; oophorectomy; bone mineral density; intima-media thickness

INTRODUCTION

Osteoporosis and cardiovascular disease (CVD) account for a large proportion of morbidity and mortality in women, most notably after the onset of menopause. The loss of ovarian function associated with menopause, specifically the decreased production of estrogen, has been linked to these conditions (1). It is generally accepted that women with premature ovarian failure or early oophorectomy are at increased risk for osteoporosis and cardiovascular disease compared to women undergoing menopause at the expected time period(2). However, whether or not the absence of ovaries specifically during the postmenopausal years has an adverse effect on progression of these conditions is not fully documented (3).

Bone is a dynamic tissue, undergoing constant remodeling and repair. While a woman's peak bone mass is achieved by approximately 19 years of age, the period of greatest bone loss is associated with the drastic drop in estrogen levels during menopause(4). Osteoporosis is a biological process characterized by loss of both bone mass and quality, leading to increased risk of fracture. The preferred method for diagnosing osteoporosis is bone densitometry using Dual-energy X-ray absorptiometry (DEXA) of the lumbar spine and hip. The cost for direct care of approximately 2 million fractures caused by osteoporosis was estimated to be \$17 billion in 2005, and is projected to increase to \$25.3 billion in 2025; the majority of these fractures and their costs of inpatient, outpatient and long-term care components were incurred by women (5). Fractures of the hip can be particularly devastating; only 44% of women older than 80 years are able to walk independently 1 year after hip fracture, and 13% of women die due to complications of hip fracture within 1 year of hospital discharge(6). Therefore, prevention of osteoporosis has great public health consequences.

While osteoporotic fractures cause significant morbidity in postmenopausal women(7), CVD continues to be the leading cause of mortality in women, specifically in those greater than 65 years of age(8). A postmenopausal woman is more likely to die from CVD than from cancer, chronic lower respiratory disease, and Alzheimer's disease combined (9). B-mode ultrasonographic measurement of carotid artery intima-media thickness (CIMT) has been proven to be a safe, noninvasive, and a relatively inexpensive correlate of CVD risk, as well as a quantifiable measurement of subclinical atherosclerosis (3, 10, 11). Identifying women at risk for CVD and subsequently monitoring their disease progression with CIMT measurements may help guide use of therapeutic interventions.

Several studies have compared women with oophorectomy to age-matched women with intact ovaries, and evaluated the effect of oophorectomy on both bone and cardiovascular

health. In 2009, Rivera et al conducted a cohort study with long-term follow-up of 1091 women with bilateral oophorectomy prior to age 45 and age-matched women without oophorectomy and concluded that bilateral oophorectomy was associated with increased CVD-related mortality (10, 12). Despite the fact women were evaluated long into menopause, time since menopause was not controlled for. Given that those women having undergone bilateral salpingo-oophorectomy were menopausal for a longer period of time than the age-matched ovary-retaining comparison group, it is relevant to make comparisons based on time since menopause.

It is also known that premature menopause either from oophorectomy or ovarian failure results in lower BMD compared to women undergoing menopause at a normal age (13, 14). Data suggest that the greatest loss in BMD occurs during the perimenopause (15). However, few studies have evaluated the effects of oophorectomy on BMD and CIMT measured long after menopause, specifically in women who have been postmenopausal for more than a decade. Importantly, due to the adrenopause, there is a decrease in function of the androgen-secreting zone of the adrenal glands with increasing age, resulting in declining levels of circulating levels of androgens provided by the adrenal glands(16). Therefore, as women age, the adrenal glands play less of a role and intact ovaries may play an increasingly important role in maintaining baseline levels of androgens and estrogens. We hypothesized that with increasing time since menopause, retained ovaries compared to oophorectomy would be associated with a protective effect on both bone loss and vascular thickening compared with menopausal women with prior oophorectomy. To address this issue, we used data from a randomized controlled trial of postmenopausal women to determine whether time since menopausal transition in oophorectomized women compared to those who retained their ovaries is associated with bone loss and progression of subclinical atherosclerosis in healthy women.

MATERIALS AND METHODS

Subjects

The Women's Isoflavone Soy Health (WISH) trial was a randomized, double-blinded, placebo-controlled trial conducted from April, 2004 to March 2009 to determine whether dietary supplementation with high-dose isoflavone soy protein reduces subclinical atherosclerosis determined by CIMT thickening (17). A total of 350 healthy postmenopausal women were enrolled from the general population of the Greater Los Angeles area for participation in the trial. Menopause was operationally defined as absence of menstrual bleeding for at least one year and serum estradiol measurements of less than 20 pg/mL. Exclusion criteria included signs, symptoms, or personal history of CVD, diabetes mellitus or fasting serum glucose greater than 126 mg/dL, fasting triglycerides greater than 500 mg/dL, systolic blood pressure greater than 160 mmHg and/or diastolic blood pressure greater than 110 mmHg, untreated thyroid disease, serum creatinine greater than 2 mg/dL, life-threatening illness with a prognosis of less than 5 years, alcohol intake of greater than 5 drinks/day or substance abuse, current use of menopausal hormone therapy or soy/nut or related food allergies. The University of Southern California Institutional Review Board approved the study protocol; all participants provided written informed consent.

Data Collection

WISH trial participants were followed for 3 years. During this time, ultrasound determinations of CIMT were assessed every 6 months as described previously (17). CIMT was evaluated as rate of change, expressed as μm per year. BMD was assessed using DEXA scans at baseline and annually thereafter. Rate of change in BMD was annualized and expressed as change rate in 1000 g per cm^2 per year. Analyses were limited to women who had determinable oophorectomy status and time since menopause data available, and; (1) had a baseline and at least 1 follow-up carotid ultrasound measurement ($n=290$ for CIMT analysis), (2) had a baseline at least 1 follow-up DEXA scan ($n=262$ for BMD analysis). Dietary isoflavone soy protein supplementation was not found to significantly reduce CIMT progression relative to placebo in the WISH trial (17). For this analysis, participants were divided by oophorectomy status. A total of 260 of these 290 participants with intact ovaries underwent randomization in the WISH trial; this included women who either underwent natural menopause or had a previous hysterectomy without oophorectomy at the time of surgery. There were 30 of 290 participants who had bilateral oophorectomy prior to WISH randomization. Participants were then categorized according to time-since-menopause into 3 categories (determined at time of randomization) – less than 5 years, between 5 and 10 years, and greater than 10 years. Participants who were less than 5 years menopausal ($n=68$) were excluded from analysis because only one participant in this group underwent oophorectomy. In the remaining menopause categories ($n=222$), between 5 and 10 years menopausal and greater than 10 years menopausal, there was a similar distribution amongst the participants who were randomized to receive isoflavone vs. placebo supplementation (Table 1). Since there were no treatment group differences in BMD or CIMT progression (17), the data from both treatment groups, isoflavone soy protein supplementation and placebo, were combined for statistical analysis.

Statistical Analysis

Associations between oophorectomy status and BMD and CIMT progression were analyzed in groups of time since menopause. Longitudinal models testing associations with annualized BMD and CIMT progression used mixed effects linear regression models. In these models, the regression coefficient associated with years since baseline (randomization) estimated the annual rate of BMD (or CIMT) progression. An interaction term of oophorectomy-by-time tested whether the progression rates differed in women with versus without an oophorectomy. Random effects were specified for a subject-specific intercept (baseline value of BMD/CIMT) and slope (progression rate of BMD/CIMT). Additional adjusting covariates included age, randomized treatment group, and randomization strata. In the combined sample, differences in the effects of oophorectomy on BMD/CIMT progression were tested by adding an interaction term (menopause stratum-by-oophorectomy-by-time). Analyses were repeated excluding subjects who took estrogen (for CIMT analyses, $n=2$ excluded) or estrogen or bisphosphonates (for BMD analyses, $n=69$ excluded) during the trial. In all analyses, a p value of <0.05 was considered statistically significant.

RESULTS

Study Sample

Characteristics of the sample are presented by oophorectomy group in Table 1.

Oophorectomized women were on average significantly younger than non-oophorectomized women ($p = 0.01$). The groups did not differ on time since menopause, randomized treatment group assignment, or CIMT level at baseline.

Bone Mineral Density

Rate of change in BMD was annualized and expressed as change rate in 1000g per cm^2 per year in all groups. Each BMD site was analyzed individually (hip, lumbar spine, and femoral neck). In all measured areas, there was a larger decline in the mean rate of BMD in oophorectomized compared to intact women; however these differences were not significantly different in either the 5-10 years since menopause or the greater than 10 years menopausal subgroups (Table 2). After excluding women who used estrogen or bisphosphonates during the trial ($n=69$), oophorectomized women showed a larger rate of decline in BMD rate than did women with intact ovaries (see Figure 1). In the lumbar spine, the BMD change was lower (greater decline) in those with previous oophorectomy in the 5-10 years menopausal group ($p=0.02$) and the trend persisted in the greater than 10 years menopausal group ($p=0.08$). In the hip, there was no difference in those 5-10 years menopausal; however, in those menopausal for greater than 10 years, there was a statistically significant difference, with less bone loss in those with ovarian conservation ($p=0.02$). Data was similar in the femoral neck, with no difference in the group 5-10 years menopausal, but with statistical significance noted in those furthest from menopause ($p=0.03$). These differences in BMD decline among oophorectomy groups did not significantly differ by time since menopause (all p -values for interaction > 0.05 ; Table 2).

Carotid Artery Intima-Media Thickness

Among women 5-10 years from menopause there was an average lower progression of CIMT in the oophorectomy group that was not statistically significant ($p=0.15$; Table 3). However, among women more than 10 years menopausal, CIMT progression was significantly higher in oophorectomized women ($p=0.03$). These associations of CIMT progression with oophorectomy status significantly differed by time since menopause (p -value for interaction = 0.02). Results were similar when estrogen use was excluded ($n=2$).

DISCUSSION

Our data suggest a beneficial role for postmenopausal ovaries in slowing the rate of bone loss and atherosclerosis. In fact, there is a doubling of the rate of bone loss and CIMT thickening in oophorectomized relative to non-oophorectomized women. Regardless of the medications that are used to treat the clinical sequelae of these conditions, oophorectomy appears to put women at higher risk of developing osteoporosis and CVD. There is a deep-rooted belief amongst many gynecologists that the ovaries completely lose function and, as a result, do not provide any protective influence on bone and cardiovascular health after menopause. In accordance with this belief, it is commonplace to offer and perform

oophorectomy at the time of pelvic surgery in menopausal or perimenopausal women. In the US, 55% of all women undergoing hysterectomy for benign indications, without increased risk of breast or ovarian cancer, have concurrent bilateral oophorectomy; this increases to 78% in those women aged 45-64(18). However, with emerging data supporting possible benefits of ovarian conservation, it may be time to reconsider this practice.

Long term follow up of the Nurses' Health Study evaluated over 29,000 women who underwent hysterectomy for benign indications and showed that compared to bilateral oophorectomy, ovarian conservation was associated with not only the obvious increased risk of ovarian cancer, but also an increase in breast cancer as well (19). However, oophorectomy in these women increased overall mortality from all causes (19). While this study did not address BMD, an increased risk for both CHD and stroke in oophorectomized women (19) is supported by our data showing that the rate of subclinical atherosclerosis progresses faster in those having undergone oophorectomy when compared to their ovary retaining counterparts. In a cross-sectional design, Ozkaya, et al, showed similar results favoring ovarian conservation on CIMT and BMD after adjusting for age and time since menopause (14).

A common contention to ovarian conservation is the risk of development of ovarian cancer with age. Currently there are no specific or reliable screening techniques available for this disease and diagnosis often occurs after the disease has reached an advanced stage. As a result, the majority of women diagnosed with ovarian cancer succumb to the disease, with a 5-year survival rate of only 31% in those with advanced stage disease(20). While being diagnosed with ovarian cancer is devastating, it accounts for only 3% of all new cancer diagnoses in women in the US(20); the lifetime risk of developing ovarian cancer is one in 70, or less than 1.5%. This is without addressing risk factors (i.e., nulliparity, family history, genetic predisposition such as BRCA-1 or BRCA-2 mutations) or protective measures (i.e., multiparity, tubal ligation, and history of hormonal contraceptive use). Given the high morbidity, mortality, and monetary burden of osteoporotic fractures and CVD, it seems prudent that women without increased risk of cancer should be counseled regarding risks and benefits of retention of their ovaries when undergoing pelvic surgery for a benign indication.

Our data illustrate that oophorectomy is detrimental for both bone and cardiovascular health long after menopause. CIMT progression and BMD loss were worse in those women greater than 10 years menopausal having undergone oophorectomy. However, statistical significance was noted only after excluding for estrogen and bisphosphonate use. This is especially clinically relevant in the current post-WHI climate, as significantly fewer patients initiate and/or continue use of HRT (21, 22) possibly contributing to excess death(23). It remains unclear as to whether this tendency is due to physician bias, patient request, or multifactorial. However, taking this trend into account, more women may be without HRT and its benefits long after the menopausal transition, where we found that the protective effect of ovarian conservation may be the greatest. Given the risks associated with initiating estrogen use in older postmenopausal patients(24), it may be prudent to suggest ovarian conservation in perimenopausal and menopausal women, especially those who are not candidates for HRT, in order to avoid these risks as women age.

Contrary to popular belief regarding the safety of bisphosphonates, there are accumulating data challenging the long term safety of bisphosphonates (24). Data have demonstrated that most significant risks of bisphosphonate usage are rare, and that practitioners should not alter their prescribing habits nor should they offer drug holidays, as the risks do not outweigh the benefits of treating osteoporosis with these medications (25-27). Implications of the climate regarding bisphosphonate use are historically similar to that of HRT use. While it is too soon to tell, such highly publicized controversy regarding the safety of bisphosphonates may alter prescribing practices, despite encouragement to continue its use for treatment of osteoporosis. If this is the case, it could have significant repercussions on the health of postmenopausal women, potentially putting them at a greater risk for fracture. Therefore, it is important to discuss the benefits of ovarian conservation on postmenopausal bone health, especially in those women who are not taking HRT or bisphosphonates, as we have shown a statistically significant worsening BMD in these women who have previously undergone oophorectomy.

Several limitations of our study are recognized, most notably the small size of the oophorectomized study population. Also, for sample size purposes our analysis combined women who had undergone natural menopause as well as hysterectomy with ovarian conservation, and compared these women to those who had a hysterectomy with bilateral oophorectomy. An improvement on study design would only compare hysterectomy with ovarian conservation to hysterectomy with oophorectomy to better evaluate the effects of ovarian conservation on BMD and CIMT in the postmenopausal woman. However, this study adds to mounting evidence that ovarian conservation should be offered, if not encouraged, to most women undergoing pelvic surgery for benign indications, regardless of their menopausal status.

In conclusion, women who have undergone natural menopause may benefit from continued residual postmenopausal ovarian function. In women without increased ovarian cancer risk and particularly in those with factors known to decrease their risk of ovarian cancer, the benefits of ovarian conservation likely outweigh the risk of ovarian cancer. It is important for physicians to thoroughly counsel their patients regarding lifelong risks and benefits of oophorectomy. There is mounting evidence that ovarian preservation is protective long into the menopause, even in those women who are many years postmenopausal.

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REFERENCES

1. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. Apr 6; 2011 305(13):1305–14. [PubMed: 21467283]
2. Dwyer KM, Nordstrom CK, Bairey Merz CN, Dwyer JH. Carotid wall thickness and years since bilateral oophorectomy: the Los Angeles Atherosclerosis Study. *Am J Epidemiol*. Sep 1; 2002 156(5):438–44. [PubMed: 12196313]

3. Mack WJ, Slater CC, Xiang M, Shoupe D, Lobo RA, Hodis HN. Elevated subclinical atherosclerosis associated with oophorectomy is related to time since menopause rather than type of menopause. *Fertil Steril*. Aug; 2004 82(2):391–7. [PubMed: 15302289]
4. ACOG Practice Bulletin N. 129. Osteoporosis. *Obstet Gynecol*. Sep; 2012 120(3):718–34. [PubMed: 22914492]
5. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. Mar; 2007 22(3):465–75. [PubMed: 17144789]
6. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int*. Feb; 2004 15(2):87–94. [PubMed: 14605799]
7. Karim R, Dell RM, Greene DF, Mack WJ, Gallagher JC, Hodis HN. Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause*. Nov; 2011 18(11):1172–7. [PubMed: 21775911]
8. Guidelines for Women's Health Care. A Resource Manual. 3 ed.. Adams Hillard JSB, Paula J.; Barss, Vanessa A.; Cowan, Bryan D.; Davis, Ann J.; Macri, Cynthia I.; Mikhail, Lyree N.; Newel, Gail J.; Perlmutter, Johanna F.; Zinberg, Stanley; Mitchell, Mary F.; Luchowski, Alicia T.; Smee, Sarah S., editors. American College of Obstetricians and Gynecologists; Washington DC: 2007.
9. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics--2013 Update A Report From the American Heart Association. *Circulation*. Dec 12, 2012
10. Negi SI, Nambi V. The role of carotid intimal thickness and plaque imaging in risk stratification for coronary heart disease. *Curr Atheroscler Rep*. Apr; 2012 14(2):115–23. [PubMed: 22281656]
11. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med*. Feb 15; 1998 128(4):262–9. [PubMed: 9471928]
12. Rivera CM, Grossardt BR, Rhodes DJ, Brown RD Jr, Roger VL, Melton LJ, 3rd, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause*. Jan-Feb; 2009 16(1):15–23. [PubMed: 19034050]
13. Gallagher JC. Effect of early menopause on bone mineral density and fractures. *Menopause*. May-Jun; 2007 14(3 Pt 2):567–71. [PubMed: 17476146]
14. Ozkaya E, Cakir E, Okuyan E, Cakir C, Ustun G, Kucukozkan T. Comparison of the effects of surgical and natural menopause on carotid intima media thickness, osteoporosis, and homocysteine levels. *Menopause*. Jan; 2011 18(1):73–6. [PubMed: 20661165]
15. Seifert-Klauss V, Link T, Heumann C, Lupp P, Haseitl M, Laakmann J, et al. Influence of pattern of menopausal transition on the amount of trabecular bone loss. Results from a 6-year prospective longitudinal study. *Maturitas*. Nov 20; 2006 55(4):317–24. [PubMed: 16781095]
16. Nawata H, Yanase T, Goto K, Okabe T, Nomura M, Ashida K, et al. Adrenopause. *Horm Res*. 2004; 62(Suppl 3):110–4. [PubMed: 15539809]
17. Hodis HN, Mack WJ, Kono N, Azen SP, Shoupe D, Hwang-Levine J, et al. Isoflavone soy protein supplementation and atherosclerosis progression in healthy postmenopausal women: a randomized controlled trial. *Stroke*. Nov; 2011 42(11):3168–75. [PubMed: 21903957]
18. Parker WH. Bilateral oophorectomy versus ovarian conservation: effects on long-term women's health. *J Minim Invasive Gynecol*. Mar-Apr; 2010 17(2):161–6. [PubMed: 20226402]
19. Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol*. May; 2009 113(5):1027–37. [PubMed: 19384117]
20. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. Jul-Aug; 2009 59(4):225–49. [PubMed: 19474385]
21. Wegienka G, Havstad S, Kelsey JL. Menopausal hormone therapy in a health maintenance organization before and after women's health initiative hormone trials termination. *J Womens Health (Larchmt)*. May; 2006 15(4):369–78. [PubMed: 16724885]

22. Steinkellner AR, Denison SE, Eldridge SL, Lenzi LL, Chen W, Bowlin SJ. A decade of postmenopausal hormone therapy prescribing in the United States: long-term effects of the Women's Health Initiative. *Menopause*. Jun; 2012 19(6):616–21. [PubMed: 22648302]
23. Sarrel PM, Njike VY, Vinante V, Katz DL. The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years. *Am J Public Health*. Sep; 2013 103(9):1583–8. [PubMed: 23865654]
24. Hodis HN, Mack WJ. The timing hypothesis and hormone replacement therapy: a paradigm shift in the primary prevention of coronary heart disease in women. Part 2: comparative risks. *J Am Geriatr Soc*. Jun; 2013 61(6):1011–8. [PubMed: 23692449]
25. McClung M, Harris ST, Miller PD, Bauer DC, Davison KS, Dian L, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. *Am J Med*. Jan; 2013 126(1):13–20. [PubMed: 23177553]
26. Bonnick SL. Going on a drug holiday? *J Clin Densitom*. Oct-Dec;2011 14(4):377–83. [PubMed: 22051091]
27. FDA. [August 12, 2013] Update of Safety Review Follow-up to the October 1, 2007 Early Communication about the Ongoing Safety Review of Bisphosphonates. 2010. [updated 3/4/2010; 2013]; Available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm136201.htm>

Capsule

Secondary analysis of the WISH trial demonstrates that as menopausal onset increases in healthy postmenopausal women, oophorectomy is associated with faster rates of bone loss and carotid artery intima-media thickening.

Figure 1.

Bone mineral density (BMD) annualized change rates (excluding estrogen and bisphosphonate use)

Table 1

Baseline characteristics by oophorectomy group

Variable	No oophorectomy (n = 193)	Oophorectomy (n = 29)	P-value *
Age, years	63.2 (6.2)	60.0 (6.6)	0.01
Ethnicity			
White (non-Hispanic)	131 (68%)	14 (48%)	0.07
Black (non-Hispanic)	9 (5%)	0 (0%)	
Hispanic	25 (13%)	8 (28%)	
Asian	20 (10%)	6 (21%)	
Other	8 (4%)	1 (3%)	
Time since menopause			
5 – 10 years	78 (40%)	10 (34%)	0.54
>10 years	115 (60%)	19 (66%)	
Randomized treatment			
Placebo	90 (47%)	17 (59%)	0.23
ISP	103 (53%)	12 (41%)	
Randomized CIMT strata			
< 0.75 mm	45 (23%)	8 (28%)	0.62
0.75 mm	148 (77%)	21 (72%)	

Mean (SD) for continuous and N (%) for categorical variables

* Oophorectomy groups compared using t-test for continuous, and chi-square test for categorical variables

Table 2

BMD annualized change rates by oophorectomy group, stratified by years since menopause

Subject group		n_1/n_2	Oophorectomy group		p-value ^a	Interaction p-value ^b
			No oophorectomy	Oophorectomy		
<u>All subjects (N=202)</u>						
Lumbar spine	5-10 years	74/9	3.94 (0.82 to 7.06)	−4.34 (−13.5 to 4.85)	0.10	0.60
	>10 years	102/17	4.22 (0.85 to 7.59)	−0.33 (−8.38 to 7.73)	0.31	
Total hip	5-10 years	74/9	−0.85 (−3.19 to 1.49)	−7.37 (−14.2 to −0.56)	0.08	0.35
	>10 years	102/17	−2.81 (−4.83 to −0.79)	−5.76 (−10.6 to −0.98)	0.26	
Femoral neck	5-10 years	74/9	−2.36 (−4.86 to 0.15)	−2.34 (−9.69 to 5.01)	0.99	0.55
	>10 years	102/17	−4.03 (−6.31 to −1.75)	−6.90 (−12.3 to −1.52)	0.33	
<u>Excluding estrogen & bisphosphonate users (N=133)</u>						
Lumbar spine	5-10 years	42/7	−0.12 (−3.52 to 3.29)	−11.2 (−19.8 to −2.53)	0.02	0.65
	>10 years	72/12	0.92 (−2.31 to 4.16)	−6.45 (−14.1 to 1.24)	0.08	
Total hip	5-10 years	42/7	−3.67 (−6.60 to −0.74)	−7.90 (−15.2 to −0.65)	0.29	0.72
	>10 years	72/12	−3.39 (−5.83 to −0.95)	−10.8 (−16.6 to −5.08)	0.02	
Femoral neck	5-10 years	42/7	−5.34 (−8.63 to −2.06)	−7.47 (−15.7 to 0.73)	0.63	0.34
	>10 years	72/12	−5.52 (−8.21 to −2.84)	−13.4 (−19.7 to −7.07)	0.03	

Numbers are mean (95% confidence interval) change rate in 1000 g/cm²/year.

n1: number of subjects in no oophorectomy group (no hysterectomy or hysterectomy only)

n2: number of subjects in oophorectomy group

^aP-value for oophorectomy group differences in BMD change rate analyzed by linear mixed effects models adjusting for age, treatment and randomization strata.^bP-value for interaction testing difference in oophorectomy effect by time since menopause

Table 3

CIMT progression rate by oophorectomy group, stratified by time since menopause

Subject group	n_1/n_2	Oophorectomy group		p-value ^b	Interaction p-value ^a
		No oophorectomy	Oophorectomy		
<u>All subjects (N=222)</u>					
5-10 years	78/10	6.50 (4.78 to 8.23)	2.73 (−2.12 to 7.59)	0.15	0.02
>10 years	115/19	4.30 (2.62 to 5.97)	9.15 (5.07 to 13.2)	0.03	
<u>Excluding estrogen users (N=220)</u>					
5-10 years	77/10	6.47 (4.72 to 8.22)	2.75 (−2.13 to 7.63)	0.16	0.03
>10 years	114/19	4.28 (2.59 to 5.97)	9.15 (5.06 to 13.2)	0.03	

Numbers are mean (95% confidence interval) C-IMT thickness change rate in $\mu\text{m}/\text{year}$ n_1 : number of subjects in no oophorectomy group (no hysterectomy or hysterectomy only) n_2 : number of subjects in oophorectomy group^aP-value for oophorectomy group differences in C-IMT thickness rate analyzed by linear mixed effects models adjusting for age, treatment and randomization strata^bP-value for interaction testing difference in oophorectomy effect by time since menopause