

Additional procedures for measuring the effect of hysterectomy on osteoporosis



TO THE EDITORS: Choi et al¹ analyzed the risk of osteoporosis in women who underwent hysterectomy using Korean insurance cohort data. The authors suggested that hysterectomy increases the risk of osteoporosis.¹ The authors performed 1:4 matching according to age, income, and region of residence to reduce the bias in their study. Despite these efforts, however, there are some problems with the study.

First, there is a possibility of selection bias in the study. The hysterectomy group in this study may contain many patients who underwent surgery for cancer, which is different from the characteristics in the control group.

The R4423~R4428 operative codes, which Choi et al claim to be oophorectomy, are actually extirpation of adnexal malignant tumors.² The R4143/R4144/R4154/R4155 operative codes refer to either lymphadenectomy or radical hysterectomy.² Thus, a significant number of women in the hysterectomy group selected with these codes had ovarian cancer or uterine cancer. Such surgeries for cancer are relatively stressful and often lead to weight loss, which is a risk factor for osteoporosis.^{3,4} Additionally, the effect of chemotherapy on osteoporosis should be considered. For this reason, it is unfair to compare the hysterectomy group that includes cancer patients with the control group that does not.

The second problem is whether the use of menopausal hormone therapy (MHT) was considered. The pathophysiology of osteoporosis in women is mostly caused by decreased estrogen production in the ovaries, which is accompanied by menopause.⁴ Therefore, the presence of menopause and the use of MHT drugs are important factors in the development of osteoporosis in women.

Choi et al insisted that the insurance data lacked information on the use of MHTs, but this was not true. Information (prescription date, period, dose, etc) on almost all MHT drugs used in South Korea, including conjugated estrogen, estrogen-progesterone combination, tibolone, etc, can be found in the insurance data. In South Korea, there are few MHT drugs that are over the counter, and some sex-hormone preparations are phytoestrogen preparations, such as black cohosh, so their effects are very limited.

In addition, a diagnosis code (N95.x, menopausal and other perimenopausal disorders) can be used to easily confirm the presence or absence of menopause in each participant. Therefore, the case-control group in this study should be adjusted for menopausal status, use of MHT drugs, and so on.

We respect the interesting research by Choi et al. However, we expect some modifications to their study to yield better results. ■

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REPLY



We thank Dr Kim and his colleagues for their interest and comments on our recent paper regarding an additional procedure for measuring the effect of hysterectomy on osteoporosis. Accordingly, we again reviewed our manuscript. We know that several gynecological cancers can negatively affect bone directly or through cancer treatment, including chemotherapy and sex-hormone deprivation therapy.¹

In this study, we did not find any participants who had undergone a hysterectomy without disease. Because we could not eliminate the effects of other treatments on osteoporosis in hysterectomy participants, we compared them with control participants who were treated for other cancers or other diseases without a hysterectomy, such as colon cancer. It could be an alternative way to adjust for the effects of cancer treatment in the hysterectomy and control groups. However, these other cancer patients were also treated in various ways and those effects could not be adjusted fairly, and these participants have other comorbidities, such as obesity, smoking, and gender differences. Additionally, it is not easy to

TABLE

Crude and adjusted hazard ratios (95% confidence interval) for osteoporosis in women who underwent hysterectomy with/without bilateral oophorectomy

Subgroup	Hazard ratio (95% CI)			
	Crude	P value	Adjusted ^a	P value
Total (n = 45,410)				
Hysterectomy (n = 9082) ^b	1.45 (1.37–1.53)	< .001	1.37 (1.29–1.44)	< .001
Control (n = 36,328)	1.00		1.00	
Hysterectomy without bilateral oophorectomy (n = 39,790)				
Hysterectomy (n = 7958) ^b	1.42 (1.34–1.51)	< .001	1.39 (1.27–1.43)	< .001
Control (n = 31,832)	1.00		1.00	
Hysterectomy with bilateral oophorectomy (n = 5620)				
Hysterectomy (n = 1124) ^b	1.60 (1.40–1.83)	< .001	1.47 (1.28–1.69)	< .001
Control (n = 4496)	1.00		1.00	

Statistical analyses were determined by a Cox proportional hazard regression model. Significance was at $P < .05$.

CI, confidence interval.

^a Adjusted model was measured for age, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, depression, and hormone replacement therapy medication dates; ^b $P < .05$.

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extract the appropriate control group owing to the limited number of participants.

It is well known that hormone replacement therapy (HRT) has a positive effect on bone metabolism.² The past medical history of the participants was evaluated using *International Classification of Diseases*, 10th revision, codes for menopause (N95) and premature menopause (N283), and we added the duration of HRT, including conjugated estrogen compounds, estradiol compounds, and tibolone as adjusting factors to control for the effect of the hormone preparations on osteoporosis.

After adjusting for total HRT duration, the adjusted HRs for osteoporosis were higher in both in the hysterectomy without bilateral oophorectomy group and in the hysterectomy with bilateral oophorectomy group (Table). These results were not different from our previous study, which did not apply HRT as an adjusting factor, but it is difficult to find all women receiving HRT using only insurance data.

We sincerely appreciate the valuable points brought up by Kim et al. ■

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