Title

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Journal

Journal of the National Cancer Institute, 110(12)

ISSN

0027-8874

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Publication Date

2018-12-01

DOI

10.1093/jnci/djy069

Peer reviewed

OXFORD

JNCI J Natl Cancer Inst (2018) 110(12): djy069

doi: 10.1093/jnci/djy069
Response

Response to H. Nabi et al.

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We agree with Nabi et al. that adiposity, as a main source of estrogen biosynthesis after menopause, can influence nuclear estrogen receptor (ER)–β expression in the lung. To approach this issue, in our data, we evaluated whether 1) adiposity measured by body mass index (BMI; self-reported weight in kilograms, divided by height in meters squared) was associated with nuclear ER-β expression and 2) the associations of sex and smoking with nuclear ER-β expression were altered after additionally adjusting for BMI. As shown here in Table 1, being overweight (BMI = 25 to 29.0 kg/m^2, $P = .66$) and obesity (BMI ≥ 30 kg/m^2, $P = .86$) were not associated with nuclear ER-β expression, compared with normal or underweight (BMI < 25 kg/m^2) overall. Among female participants, there was indication that nuclear ER-β expression was higher among women with a higher BMI, although the differences were not statistically significant after adjustment for hormone therapy and other variables (β = 1.4, 95% CI = –17.2 to 20.1, for overweight; β = 3.7, 95% CI = –17.0 to 24.3, for obesity, compared with normal or underweight). The second analysis showed that, although the precision of estimates was affected, the associations of sex with nuclear ER-β were essentially the same after BMI was entered as a categorical variable (<25, 25–29.0, and ≥30 kg/m^2) in the regression model. The regression coefficients (β) for sex, were –12.1 (95% CI = –24.3 to 0.03) for all participants, –13.0 (95% CI = –26.4 to 0.3) for ever smokers, and –14.7 (95% CI = –44.2 to 14.8) for never smokers, compared with β values before adjusting for BMI, presented in our article (–12.8, 95% CI = –24.7 to –0.9; –14.5, 95% CI = –27.6 to –1.5; and –14.0, 95% CI = –42.8 to 14.9, respectively). Additionally, the null association of smoking with nuclear ER-β expression was unchanged after adjustment for BMI. We are aware that BMI is an inaccurate measure of adiposity (1); other assessments of adiposity, including abdominal obesity, were unavailable in this study. A more accurate assessment of adiposity is warranted to determine whether obesity affects ER-β nuclear expression in lung cancer.

The study by Nose et al. cited in the letter showed that nuclear ER-β expression in adenocarcinoma was associated with better disease-free survival in a Japanese patient population (2). We are pleased to see this finding because it supports the notion that nuclear ER-β is important in lung cancer, as it can inhibit estrogen-signaled proliferation. It is important to note that the outcome in the study by Nose et al. was lung cancer recurrence. In our study, the outcome of survival analyses was mortality. The comparison between these two studies should be made with caution because a biological factor that is associated with disease recurrence is not necessarily related to mortality. Our results are consistent with the findings by Stabile et al. that cytoplasmic, but not nuclear, ER-β expression was associated with mortality (3). We refrained from performing a survival

Table 1. Association of BMI with nuclear ER-β protein expression

	Nuclear ER-β			
BMI, kg/m^2	No.	H-score, mean	β (95% CI) in linear regression	*P**
All participants†	723	129.0		
<25	317	126.4	(Ref)	
25–29.0	244	130.8	4.5 (–8.8 to 17.7)	.66
≥30	162	130.7	1.3 (–13.6 to 16.2)	.86
Males‡	323	134.7		
<25	113	132.9	(Ref)	
25–29.0	131	136.8	5.3 (–14.3 to 24.8)	.60
≥30	79	132.9	–0.8 (–23.0 to 21.5)	.95
Females‡,§	400	124.2		
<25	204	122.8	(Ref)	
25–29.0	113	123.8	1.4 (–17.2 to 20.1)	.88
≥30	83	128.6	3.7 (–17.0 to 24.3)	.73

*P values were calculated using linear regression t test and were two-sided. BMI = body mass index; CI = confidence interval; ER = estrogen receptor.
†Linear regression adjusting for age, race, sex, smoking.
‡Linear regression adjusting for age, race, smoking.
§Additionally adjusted for menopausal status and hormone therapy (HT) use (premenopausal, postmenopausal with never use of HT, postmenopausal with ever use of HT).

Received: March 2, 2018; **Accepted:** March 16, 2018

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analysis for nuclear ER-β expression stratified by sex because current evidence does not suggest that the associations of hormone receptors with outcomes in lung cancer patients are sex-specific (2,3).

Note

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References

1. Heymsfield SB, Peterson CM, Thomas DM, et al. Why are there race/ethnic differences in adult body mass index-adiposity relationships? A quantitative critical review. *Obes Rev*. 2016;17(3):262–275.
2. Nose N, Sugio K, Oyama T, et al. Association between estrogen receptor-beta expression and epidermal growth factor receptor mutation in the postoperative prognosis of adenocarcinoma of the lung. *J Clin Oncol*. 2009;27(3):411–417.
3. Stabile LP, Dacic S, Land SR, et al. Combined analysis of estrogen receptor beta-1 and progesterone receptor expression identifies lung cancer patients with poor outcome. *Clin Cancer Res*. 2011;17(1):154–164.

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