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Short review

# Response to the comments by Per E. Lønning

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We thank Per E. Lønning for his comments and interest in our study [1]. It is true that when analyzing low estrogen concentrations after the menopause or tissues with a high content of lipids, a careful prepurification of the sample as well as a sensitive and specific analytical method is needed. In addition to the present mass spectrometric estrone method [1], we have recently reported estradiol levels in subcutaneous adipose tissue from the breast by a validated LC-MS/MS method in the same women [2]. Moreover, serum estradiol and estrone concentrations may be measured in the same run by LC-MS/MS [3], and studies are going on in our laboratory to further improve the sensitivity of the estrogen methods. It would also be of interest to study adipose tissue levels of estrone sulfate, since Paatela et al. showed recently that steroid sulfatase, the enzyme that also hydrolyzes estrone sulfate, is active in postmenopausal human adipose tissue [3].

Estrogens seem to be concentrated in breast tissue or breast cyst fluid as compared to serum levels, except for pregnant or lactating women in whom no such gradient was reported [4]. We agree that this accumulation may be due to local synthesis in the breast or uptake from the circulation. However, different from Lønning and colleagues who compared estrogen levels in cancerous or benign breast tissue [5], we have studied nonmalignant adipose tissue from the subcutaneous compartment of the breast [1,2]. It is generally accepted that after the menopause estrogens are synthesized in adipose and other peripheral tissues and the circulating levels merely reflect the local estrogen metabolism in tissues [6,7]. If the relatively high estrogen concentration in postmenopausal adipose tissue would result from accumulation of lipophilic estrogens partly synthesized elsewhere in the body, this would happen against a concentration gradient. It is known that the cellular uptake of the circulating hydrophilic estrone sulfate occurs through active transport by organic anion transporter proteins [8]. Moreover, the lipophilic steroid fatty acyl esters incorporated into lipoprotein particles may be internalized into the cell by lipoprotein receptors [9,10]. The circulating concentration of estradiol fatty acyl esters in postmenopausal women is, however, very low [2], and thus cannot explain the much higher tissue versus plasma concentrations of estradiol. Finally, the tissue-specific regulation of aromatase expression or activity may explain the lack of correlation between local aromatase mRNA expression and concentration of estrogen in breast tissue samples or plasma [11].

## Conflicts of interest

VV, MJT, and EH have nothing to declare.

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