S23. Breast density and female hormone profiles

R. Kaaks*
German Cancer Research Center (DKFZ), Heidelberg, Germany

Elevated mammographic density – a measure of the amounts of radio-dense, fibro-glandular tissue in the breast – is a relatively strong risk factor for breast cancer. Up to six-fold increases in breast cancer risk have been observed for highest *versus* lowest density categories, independently of other major risk factors, such as age, BMI, age at first full-time pregnancy or family history of breast cancer. Changes in breast cancer density over a three-year period have also been associated prospectively with parallel changes in breast cancer risk. Because of these observed relationships, it has been proposed that mammographic density could be used as an intermediate surrogate marker for the effects of hormones on breast cancer risk. Increased density reflects increased volumes of stromal and epithelial tissues, and might also reflect increased epithelial hyperplasia, which in turn could be due to hormonal exposures.

Cross-sectional studies have shown increased mammographic densities among women using postmenopausal hormone replacement therapy (HRT). Particularly combined estrogen-plus-progestin regimens appeared to increase breast densities, more than regimens based on estrogens alone. These observations parallel those from other epidemiological studies, which have shown associations also of breast cancer risk with HRT composed of estrogens plus progestins, but not with HRT composed of estrogens only. Furthermore, in intervention trials with breast cancer patients, the selective estrogen receptor modulators ("SERMs") tamoxifen and raloxifene, which exert anti-estrogenic actions, have been observed to reduce mammographic densities, as well as risk of breast tumour recurrences.

By contract, preliminary studies did not show any clear effect of the aromatase inhibitor letrozole on mammographic density. Furthermore, relationships of mammographic density with levels of endogenous sex hormones are unclear. In several large cross-sectional studies, mammographic densities – expressed either as relative density or in terms of absolute areas of dense tissue on the mammograms – were found to be either positively or negatively associated with serum levels of estrogens (estrone, estradiol), and in some other large studies not associated at all. Regarding serum androgens (androstenedione, testosterone), no associations with mammographic density measures was found at all, but moderately positive associations were observed between density measures and serum levels of sex hormone-binding globulin (SHBG), a carrier protein that strongly binds plasma estradiol and testosterone, reducing the availability of these hormones to target tissues. Overall, these observations contrast with those from prospective studies on breast cancer risk, which was found to be directly related to serum levels of both androgens and estrogens, and inversely related to serum SHBG.

Another puzzling observation is that mammographic density has been associated equally with risks of both estrogen receptor (ER-) positive and negative breast tumours, whereas endogenous estrogens appear to be associated more strongly with risk of ER-positive tumours. ER-negatives and positive tumours combined, however, in one prospective study circulating sex steroid levels and mammographic density were independently associated with breast cancer risk in postmenopausal women, with a roughly tenfold increase in risk for women who had both elevated breast densities and elevated serum testosterone.

These observations leave doubt as to whether elevated mammographic density can be seen as an intermediate phenotype between female (endogenous) sex hormone profiles and breast cancer risk. However, mammographic densities and endogenous hormones may usefully complement each other in breast cancer risk prediction models.