Stefanie Liedtke
Dr. sc. hum.

Physical Activity and Body Weight-Related Factors: Joint or Independent Links to Postmenopausal Breast Cancer via Endogenous Sex Hormones?

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktormutter: Frau Prof. Dr. rer. nat. K. Steindorf

Strong epidemiological evidence indicates that women can reduce their postmenopausal breast cancer risk with physical activity. In contrast, being overweight or obese has been identified to increase the risk. Although the biological mechanisms are still poorly understood, in both cases endogenous sex hormones and their major protein carrier sex hormone-binding globulin (SHBG) are thought to play crucial mediating roles; accumulating evidence suggests additional involvement of the polypeptide hormone prolactin. Whereas associations between these biomarkers (except prolactin) and postmenopausal breast cancer risk are fairly well-established, several uncertainties remain regarding their association with physical activity and excess body weight.

This dissertation presents results from a cross-sectional study among 1,260 postmenopausal women recruited as controls in the breast cancer case-control study MARIE. Participants' serum levels of estrone, estradiol, androstenedione, testosterone, SHBG, and prolactin were measured. In multivariate adjusted generalized linear models, statistical associations between the biomarker levels and self-reported leisure-time physical activity (i.e., recent total leisure-time physical activity, sports activity, day-to-day bicycling, and day-to-day walking) were investigated. Given that biosynthesis of sex hormones occurs primarily in adipose tissue after menopause, the analyses focused primarily on confounding and effect modification by body weight-related factors [i.e., body mass index (BMI), waist and hip circumference, and waist-to-hip ratio (WHR)]. In addition, associations of body weight-related factors with sex hormones, SHBG, and prolactin were investigated more thoroughly. The principle aim of these analyses was to assess confounding and effect modification by BMI in observed associations of biomarker levels with proxy measures for an abdominal (waist circumference, WHR) and gluteofemoral (hip circumference) fat distribution.

The analyses revealed that higher levels of sports activity were significantly associated with lower levels of estrone and total and free testosterone. All associations remained significant after further controlling for BMI or any other body weight-related factor. However, associations responded differently to the adjustment. Results suggest a greater impact of BMI on the association between sports activity and levels of estrone and free testosterone than on the association between sports activity and levels of total testosterone. Data did not indicate effect modification by BMI, waist circumference, hip circumference, or WHR in these associations. No physical activity variable was significantly related to levels of total and free estradiol, androstenedione, SHBG, or prolactin.

The results suggest that long-term sports activity performed after menopause reduces circulating blood levels of estrone and total and free testosterone. While effects on estrone and free testosterone seem to be largely mediated by sports-induced BMI reductions, effects on total testosterone appear to be mainly independent of this mechanism. The observed BMI-independent associations might partly explain the frequently reported BMI-independent inverse association between physical activity and postmenopausal breast cancer risk.

All body weight-related factors showed a significant positive association with levels of all estrogens and free testosterone and a significant negative association with SHBG. Except WHR, the factors were also significantly related with total testosterone. After controlling for BMI, all associations of hip circumference with the biomarkers were reduced to a nonsignificant level. Relationships of waist circumference and WHR with the biomarkers became weaker, but both factors still showed significant associations with levels of free estradiol, free testosterone, and SHBG. In stratified analyses, these associations were significant in women with a BMI <30 kg/m^2, whereas in obese women, a possible unique effect of abdominal fat on the biomarkers appeared to be masked by the already large amount of overall body fat. Overall, these results indicate that after menopause an abdominal but not gluteofemoral fat distribution is associated with levels of SHBG and SHBG-related sex hormones, independent of BMI. This finding, in turn, supports a BMI-independent association between an abdominal fat distribution and postmenopausal breast cancer risk mediated by these biomarkers.

Results of a direct comparison drawn in this dissertation suggest that BMI alterations influence blood circulating levels of sex hormones and SHBG more strongly, in general, than alterations in sports activity. Data indicate comparably strong influences of both BMI and sports activity only on total testosterone levels. Levels of androstenedione and prolactin, in turn, seem to be influenced neither by physical activity nor body weight-related factors.

In summary, both physical activity and body weight-related factors were associated with circulating levels of several sex hormones in this study. Moreover, associations of sports activity were in part yet not fully mediated by concurrent associations with BMI. Results subsequently support the hypothesis that both physical activity and body weight-related factors influence postmenopausal breast cancer risk via endogenous sex hormones, at least partly, and that they exert joint as well as independent effects via these biomarkers. However, to completely understand the mechanisms linking physical activity and body weight-related factors to breast cancer risk, relationships with other known and suspected breast cancer-related biomarkers also warrant further investigation.