Rebecca Ellen Ritte
Dr.sc.hum

Hormonal, reproductive and life-style characteristics and risk of major breast cancer sub-types in the EPIC Cohort

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)

Doktorvater: Prof. Dr. Rudolf Kaaks

Breast cancer is a complex disease with a variety of histo-pathological and molecular sub-forms with diverse clinical outcomes. One important sub-classification of clinical breast tumors is based on the presence or absence of estrogen (ER) and progesterone (PR) receptors. The routine assessment of ER and PR guides targeted therapies and provides important prognostic information. The expression of the hormone receptors also broadly overlaps with more detailed molecular sub-classifications of breast tumors (such as luminal A or B, basal type, triple negative or normal-like breast cancers) as determined by microarray-based gene expression profiling.

Epidemiological data indicate that the associations of lifetime exposures to estrogens, such as postmenopausal adiposity levels, an early age at menarche, late age at menopause, and endogenous hormone use, with risk of hormone receptor-positive tumors are reasonably well characterized; however, uncertainty remains regarding the etiology of hormone receptor-negative malignancies. The inconsistent results are mainly because of the heterogeneous nature of the hormone receptor-negative subtypes and previous prospective studies have lacked sufficient sample sizes.

The analyses within this thesis were based on the 2010 follow-up data from the EPIC cohort and investigated the association of excess adiposity (BMI, waist and hip circumference), adult indicators of childhood growth and sexual maturation (adult attained height, leg length, sitting height and age at menarche) and reproductive factors (the time between menarche and first full-term pregnancy, parity, age at first and last birth, breast feeding, age at menopause and HRT and OC use), with risk of hormone receptor-negative and/or positive breast cancer. In addition, a nested case-control study was completed to investigate the association of endogenous sex hormone levels (estradiol, testosterone and sex hormone binding globulin) with the risk of breast cancer by hormone receptor status. The study included the largest sample to date of European breast cancer cases in women; a total of over 7000 incident cases of breast cancer with information on ER and/ or PR status.

Of the 20 EPIC centers in 10 European countries that contributed data regarding ER and PR, 75.2% of cases had information on ER status and 62.0% on PR status. Approximately, 80% of the tumors were ER-positive and 64% were PR-positive, strongly following the proportions reported by cancer registries. The incidence of both hormone receptor-negative (ER-negative, PR-negative or ER-PR-) and hormone receptor-positive (ER-positive, PR-positive or ER-PR-) tumors increased with age. However after the age of 50, rates of hormone receptor-negative disease no longer increased with

advancing age, whereas the incidence rates of hormone receptor-positive tumors continued however at a reduced pace compared to earlier ages. The change in the age-related rise in incidence rates after age 50 suggested a possible relationship of both receptor-negative and positive breast cancer with the menopause-related cessation of ovarian estrogen and/or progesterone synthesis.

The statistical analyses showed that increased general adiposity among postmenopausal women was associated with risk of receptor-negative tumors, however only in never users of HRT. Furthermore, women who reported current HRT use at baseline were at an increased risk of both receptor-negative and positive breast cancer, although this increase was stronger for receptor-positive tumors. In both receptor-negative and positive malignancies, a stronger HRT-related increase in risk among leaner than among more obese women was observed.

The positive association of standing height and leg length and the inverse association of menarcheal age were also associated with both hormone receptor-negative and positive breast tumor types, indicating that exposures during rapid growth periods are reflected in risk association of both breast cancer subtypes. The influence of faster growth and earlier sexual maturation during childhood and puberty may establish long-term risk profiles for both receptor-negative and positive malignancies. The stronger association of sitting height than leg length with hormone receptor-positive tumors suggested a possible hormonal/metabolic link that could be more specific for postmenopausal women and could be independent of risk patterns recognized during childhood. Factors leading to height loss suggested a possible hormonal link that could be more specific for postmenopausal women.

Similar risk associations were also observed for both receptor-negative and positive breast tumors with increasing menarcheal age, time between menarche and first full-term pregnancy and increasing number of pregnancies The differential relative risk of a longer cumulative duration of breast feeding between women who had early first full-term pregnancy and a late first full-term pregnancy could be due to the period of time the undifferentiated breast tissue is exposed to carcinogenic influences and the involution of breast tissue after breast feeding at an older age. The increased risk association of a longer duration of OC use with receptor-negative tumors adds further evidence of the role of sex hormones in the etiology receptor-negative tumors.

In the nested case-control study, the role of sex hormones in the etiology of receptor-negative breast cancer was further supported by the observation that, within postmenopausal women, serum androgens and estrogens were associated with risks of hormone receptor-negative as well as receptor positive breast tumor subtypes.

Using data from the EPIC study, the analyses in this thesis showed that hormone related risk factors, known to be associated with hormone-responsive breast cancer, were also associated with hormone receptor-negative breast tumors, although not of the same magnitude. The analyses have provided evidence for a possible role of sex hormones in the etiology of harder to treat and more aggressive breast cancer subtypes. However, further research is needed to establish through which molecular pathways, and during which evolutionary stages of development, androgens and estrogens can promote the occurrence of both receptor-negative and positive clinical breast tumors.