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Titel der Dissertation: Endometrial Cancer - An Analysis of Hormonal and Inflammatory Risk Factors in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Although a western lifestyle is a well-established risk factor for endometrial cancer, the mechanisms underlying this relationship still have been only partially resolved. Most of the epidemiological factors that have been associated with endometrial cancer risk are known determinants of endogenous estrogen levels and therefore support the "unopposed estrogen" hypothesis, which states that high levels of bioavailable estrogens, when not counterbalanced by progesterone, increase endometrial cancer risk. However, other biological pathways, such as the insulin axis, have already been related to endometrial carcinogenesis and, more recently, chronic inflammation has been speculated as a possible alternative independent mechanism involved in endometrial cancer development.

The aims of this thesis were to examine the associations between lifestyle determinants of endogenous hormone levels, such as smoking and reproductive factors, and endometrial cancer risk, and to address the hypothesis that factors involved with low-grade inflammatory states are, in addition or in conjunction with estrogens, related to endometrial cancer risk.

The study questions were examined within EPIC, a large scale ongoing prospective cohort study conducted across 10 European countries with information on dietary and lifestyle habits, anthropometry and with baseline blood samples available. Hazard ratio (HR) and 95% confidence intervals (CI) for endometrial cancer by categories of smoking variables and reproductive factors were calculated using Cox proportional hazard models and further adjusted for other known risk factors. After having tested and compared different assays to measure the inflammatory markers, a case-control study was nested within the EPIC cohort to analyze the effects of circulating levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), tumor necrosis factor-α (TNF-α) and soluble TNF receptors (sTNFR1 and sTNFR2) on endometrial cancer risk. A total of 342 endometrial cancer cases and 644 individually matched controls were analyzed using conditional logistic regression to estimate odds ratios (OR) and 95% CI. Using data already collected within the same case-control set on biomarkers in the estrogen, androgen, insulin and lipid pathways, together with the newly measured inflammatory markers, uncorrelated physiologic profiles were determined using factor analysis and the contribution of these profiles to endometrial cancer risk was assessed.

Reproductive factors and endometrial cancer risk
A reduction in endometrial cancer risk was observed with late menarche, early menopause, oral contraceptive (OC) use, high parity, and shorter time since last full term pregnancy (FTP). No association with risk was found for duration of breast-

feeding after adjustment for number of FTP, or for abortion (spontaneous or induced). A shorter menstrual lifespan and/or successive pregnancies implicate a shorter exposure to estrogens unopposed by progesterone, a lower mitotic activity of endometrial cells and a decrease in endometrial cancer risk. However, when all factors were considered simultaneously the association of parity was stronger than expected from suppression of menstrual cycles alone. This and the protection observed for shorter time since last pregnancy might be due to clearance of malignant cells by high progesterone levels experienced during the pregnancy.

Smoking and endometrial cancer risk

In postmenopausal women, the data showed a 22% reduction in risk for current smokers vs. never smokers and a 51% reduction for heavy smokers of more than 15 cigarettes per day, whereas in premenopausal women a statistically significant increase in risk was observed among current smokers compared to never smokers (HR: 1.75, 95%CI: 1.13-2.70). Premenopausal current smokers with the highest duration (more than 30 years) and intensity (more than 15 cigarettes per day) of smoking had a greater than 2-fold increased risk of developing endometrial cancer. EPIC is the first prospective study to show an adverse effect of cigarette smoking on endometrial cancer in premenopausal women. Smoking may have a direct toxic effect on the ovaries and premenopausal smoking women may have an increased risk of ovarian dysfunction, ovarian failure and subsequent progesterone deficiency, physiological disorders that are believed to play a major role on endometrial cancer in premenopausal women. The reduction of endometrial cancer risk observed among postmenopausal women does not have direct public health relevance since cigarette smoking is the main known risk factor for cancer and have negative consequences in several other diseases.

Inflammation – an alternative mechanism in endometrial carcinogenesis?

Circulating levels of CRP, IL-6 and IL-1Ra were significantly associated with endometrial cancer risk, although the association was largely dependent on levels of adiposity. The association between adiposity measurements and endometrial cancer was also substantially attenuated after adjustment for inflammatory markers, even when the effects of insulin or estrogens were already taken into account. The present study also showed a positive association between TNF-α and sTNFRs and endometrial cancer risk. The association for TNF-α persisted after adjustment for BMI and other confounders (OR: 1.73, 95%CI: 1.09-2.73 for 3rd vs. 1st tertile of TNF-α).

Moreover, using factor analysis, we identified four uncorrelated dimensions among a set of 20 correlated markers that could be labeled as the “insulin resistance/metabolic syndrome” (IR/MS), “steroids”, “inflammation” and “lipids” factors. Three independent components (“IR/MS”, “steroids” and “inflammation”) seemed to be associated with endometrial cancer risk. The “lipids” component, apart from its contribution to the metabolic syndrome, was not significantly associated with endometrial cancer risk. After BMI adjustment, the magnitude of the associations in postmenopausal women for the “IR/MS” and the “steroids” factors was very similar; the estimates for the “inflammation” factor were attenuated and no longer statistically significant.

These data further support the idea that, besides the well-known steroids and insulin resistance/metabolic syndrome axes, inflammation plays an important role in endometrial carcinogenesis. Inflammation may influence endometrial carcinogenesis through indirect obesity-related effects such as their implication in the development of insulin resistance or the modulation of aromatase activity by cytokines within the adipose tissue or within the endometrium. It is also possible that cytokines have a direct effect on endometrial carcinogenesis through the NF-κB pathway.

So far, this is the first study of its kind and further prospective studies are needed to confirm these observations. Further experimental studies should also investigate whether inflammation has a direct and independent effect on endometrial carcinogenesis.

The results of the present thesis first demonstrate a possible role of inflammation as a third independent axis, in addition to sex-steroids and insulin, in the association between a western lifestyle and endometrial cancer risk. Modifiable lifestyle factors that might influence endogenous levels of circulating hormones, metabolic and inflammatory factors are therefore are therefore important to consider with respect to the risk of developing endometrial cancer.