1

BREAST TUMOR PROLIFERATION IN RELATION TO BREAST CANCER RISK FACTORS. N. Oestreicher,* K.E. Malone, and P.L. Porter (Fred Hutchinson Cancer Research Center, Seattle, WA 98109)

Ki-67 is an antibody that recognizes a protein expressed in cells that are actively dividing and is thus a measure of tumor cell proliferation. Personal characteristics that influence breast tumor etiology may also affect tumor proliferation, but previous studies have been contradictory and lacked a formal statistical approach. We examined the association between breast cancer risk factors and breast tumor proliferation in 334 women 40 years of age and older diagnosed with invasive breast cancer between 1988 and 1994. Ki-67 (percent of Ki-67 positive tumor cells averaged over four readings) was log-transformed and analyzed in a linear regression model with the exponentiated regression coefficient $\beta(e^{\beta})$ as the measure of association. Mitotic count was dichotomized into high/intermediate vs. low and analyzed in an unconditional logistic regression model with the odds ratio (OR) as the measure of association. The results of these two models substantively agreed. Consistent with other studies, there was a significant trend of decreased proliferation with older age at diagnosis (ORs: 40-49 years: 2.58; 50-59 years: 1.61; 60-69 years: 1.31; 70-79 years: 1.00; 80+ years 1.00, p-trend: 0.01). We also found increased proliferation in tumors of Black women compared to white women, adjusted for age at diagnosis (e^{β}1.46, 95% CI 0.71-2.99). In contrast to previous studies, we found no association between use of hormone replacement therapy and cell proliferation. Further investigation is needed into the specificity of tumor proliferation measures.

2

SERUM ORGANOCHLORINE LEVELS AND BREAST CANCER: A NESTED CASE-CONTROL STUDY OF NORWEGIAN WOMEN. E.M. Ward,* P. Schulte, B. Grajewski, A. Andersen, D.G. Patterson Jr., W. Turner, E. Jellum, J.A. Deddens, J. Friedland, N. Roeleveld, M. Waters, and M.A. Butler (National Institute for Occupational Safety and Health, Cincinnati, OH 45226)

This study investigated the potential association between organochlorine exposure and breast cancer, utilizing stored sera collected in 1973-1991 from the Janus serum bank in Norway. Breast cancer cases were ascertained prospectively from among 25;431 female serum bank donors. A total of 150 controls were matched to cases by dates of sample collection and birth. One gram of serum from subject was analyzed for a total of 71 organochlorine compounds. Six pesticides (*B*-HCCH, heptachlor epoxide, oxychlordane, trans-nonachlor, DDE, and p,p'-DDT) and 26 individual PCB congeners had >90% of samples over the limit of detection. There was no evidence for higher mean serum levels among cases for any of these compounds, or any trend of increasing risk associated with higher quartiles of exposure. The remaining compounds (including dieldrin) were analyzed with respect to proportion of cases and controls having detectable levels. Our study did not confirm the recent findings of a Danish study of increased concentrations of dieldrin in serum of breast cancer cases. The evidence to date on the association between serum organochlorines is not entirely consistent, but there is accumulating evidence that serum levels of DDE and total PCBs are not important predictors for breast cancer in the general population. Studies to date have not been able to evaluate whether exposure to highly estrogenic, short-lived PCB congeners increases breast cancer risk, nor have they fully evaluated the risk associated with organochlorine exposure in susceptible subgroups or at levels above general population exposure, including women with occupational exposure.

3

A POLYMORPHISM IN THE CATECHOL-O-METHYL TRANSFERASE GENE AND RISK OF BREAST CANCER. SE Hankinson,* WC Willett, GA Colditz, FE Speizer, and DJ Hunter, for the NHS Research Group (Harvard University, Boston MA 02115)

Estrogen metabolites are hypothesized to influence risk of breast cancer. A functional polymorphism in the catechol-O-methyl transferase [COMT] gene (G to A transition at codon 158), which is involved in estrogen metabolism and results in 4-fold differences in enzyme activity, is of interest. We evaluated the relation between COMT and breast cancer risk in a nested case-control study conducted within the Nurses' Health Study. Blood samples were collected in 1989-90; up to June 1994, we identified 462 cases of breast cancer. One to two controls were selected per case, matched on age and month and time of day of blood collection, for a total of 620 controls. In conditional logistic regression, controlling for a number of breast cancer risk factors, we observed no association between genotype and risk of breast cancer (LL versus HH [reference]: relative risk (RR) = 0.85, 95% confidence interval (CI) = 0.59-1.21); similar associations were noted when stratified by menopausal status (premenopausal: RR = 0.90, CI = 0.29-2.80; postmenopausal: RR = 0.88, CI = 0.59-1.31). Results were did not vary substantially when evaluated according to category of body mass index, family history of breast cancer, or a range of other breast cancer risk factors. Postmenopausal plasma levels of estradiol and estrone also were unrelated to genotype. Our data do not support an important association between this polymorphism and breast cancer risk.

4

ALCOHOL CONSUMPTION AND INCIDENCE OF BENIGN BREAST DISEASE. C Byrne,* PM Webb, TW Jacobs, G Peiro, SJ Schnitt, JL Connolly, WC Willett, and GA Colditz (Channing Laboratory, Harvard University, Boston, MA 02115)

Moderate alcohol consumption has been recognized to be associated with increased risk of developing breast cancer. Benign breast disease (BBD), particularly proliferative conditions, are often considered as potential "precursors" or markers for the development of breast cancer. This study evaluated the association between reported alcohol consumption and BBD incidence among 76,339 participants in the Nurses' Health Study II. Between 1989 and 1997, 16,849 women reported a first diagnosis of BBD (3,088/100,000 person-years), of which 3,165 were confirmed by tissue biopsy (580/100,000 person-years). From the pathology review for 1,469 women, 534 had nonproliferative benign breast conditions, and 935 had proliferative conditions. Pooled logistic regression for grouped failure times provided estimates of the rate ratios and 95% confidence intervals controlling for other covariates. Consumption of alcohol in did not increase BBD incidence. Compared to women who did not drink alcohol, those who consumed <5g/day had a rate ratio (RR) of 0.97 (95% confidence interval (CI): 0.9 - 1.0), 5-14.9 g/day had a RR of 0.91 (95% CI: 0.9 - 1.0), and 15+g/day had a RR of 0.86 (95% CI: 0.8 - 0.9) for any-reported BBD. Likewise, the RR for biopsy confirmed BBD was 0.99 (95% CI:0.9-1.1) for < 5g/day, 0.99 (95% CI: 0.9 - 1.1) for 5-14.9 g/day, and 0.92 (95% CI: 0.8 - 1.1) for 15+g/day. The RR for any proliferative benign condition was 0.96 (95% CI: 0.8 - 1.1) for < 5g/day, 0.81 (95% CI: 0.7 - 1.0) for 5-14.9 g/day, and 0.95 (95% CI: 0.7 - 1.3) for 15+g/day, compared to non-alcohol drinkers. This study suggests that the effects of alcohol on breast cancer risk do not appear to work through increasing the risk of proliferative benign breast disease.

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