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The Association between Tobacco Exposure and Breast Cancer Risk considering potentially modifying Effects of specific Genotypes

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A population-based case-control study was conducted in southern Germany in 1992-1995 including women with primary invasive or in situ breast tumors by age 50 and two controls matched by age and study region. The women completed a self-administered questionnaire pertaining to relevant breast cancer risk factors and provided blood samples. Participants were recontacted in 1999-2000 for a detailed telephone interview on lifetime active and passive smoking habits. The collected blood samples were genotyped for three primary genes involved in tobacco smoke metabolism, i.e. *NAT2, GSTM1*, and *CYP1A1*.

Lifetime active smoking was assessed allowing for numerous changes in smoking habits. Ever active smoking increased breast cancer risk by 30%, current active smoking by 50% when compared to never active/passive smoking. Longer, more intense active exposure increased risk, whereas risk for ex-smokers decreased with longer duration since smoking cessation. Breast cancer risk was higher for women who started smoking after age 18 or after their first pregnancy than for women who started smoking before then. Preceding studies which had also assessed lifetime active and passive smoking had reported an about two-fold increase in risk for active exposure. The higher risk for later age at onset of smoking or smoking after pregnancy is not supported by the literature, whereas results related to longer and more intense exposure and time since cessation of smoking are consistent with previous reports.

Passive smoking was assessed for childhood and adulthood residence households and for workplaces. Ever passive smoking increased breast cancer risk by 60% and contrary to active smoking, it made no difference whether exposure had taken place in the last ten years or only before then. However, breast cancer risk differed by timing of exposure in relation to childhood/adulthood or first pregnancy. Childhood exposure only and exposure only before first pregnancy were not associated with risk, whereas adulthood exposure and exposure after

first pregnancy were associated with significantly increased risks by about two-fold. Duration in years of exposure was not associated with risk, however, the measurement in hours per day years which includes intensity of exposure showed significantly increased breast cancer risks with longer, more intense passive exposure. Previous literature reports are in accordance with the results reported here, with the exception of the association between risk and timing of exposure. Existing data on timing especially in relation to pregnancies is rare and possible comparisons are therefore limited. Breast tissue is hypothesized to be most susceptible to carcinogens at younger ages which is incompatible with the obtained result of the present study. A clarification of this issue is of importance in further studies and indicates the need for an assessment of lifetime tobacco exposures.

In order to investigate joint effects of active and passive exposures participants were grouped into seven categories with respect to their combinations of exposure, dichotomizing high and low exposures by packyears of active smoking and hours per day years of passive smoking. Women with passive exposure only and the combination of high active/ high passive exposure had significantly increased risks of breast cancer by 60% and 80% respectively, whereas the other combinations had risks around unity. The assessment of joint effects has not been previously performed and the reported results can therefore not be compared with preceding literature. The obtained results of this study indicate that an investigation of joint effects may be of importance and should be further explored.

Women who had completed the self-administered questionnaire and telephone interview, had provided a blood sample, and were of German descent were included in the genetic-epidemiologic study of modifying effects by gene variants on the association between tobacco exposure and breast cancer risk. Some genotypic subgroups seem more susceptible to breast cancer when exposed to either passive or active smoke. Current active smoking increased risk in *NAT2* slow acetylators by 70% while risk was around unity for rapid acetylators when compared to never active/passive smokers. Passive exposure on the other hand was associated with a two-fold increased risk in rapid acetylators and a risk around unity in slow acetylators. There was no difference in risk by *GSTM1* genotype for active smoking, but passive smoking was associated with a higher risk in *GSTM1* carriers than *GSTM1*-null carriers. A comparison to never active/passive smokers yielded significantly increased risks for passive and for current active smoking for *CYP1A1* wildtypes, while these risks were around unity for *CYP1A1* mutant carriers. Results are partly consistent with previous reports, however, studies considering the modifying effects of gene variants on the association between tobacco smoke and breast cancer are rare and these issues need further verification in

subsequent studies. The question of which genes are involved in the association between tobacco exposure and breast carcinogenesis and which genotypic subgroups are most susceptible remains to be explored, but it seems likely that some subgroups are at a higher risk. A genetic profile may in future improve the assessment of a woman's individual risk of breast cancer when she exposes herself to tobacco smoke.

Important on the population level is that regardless of genotype active as well as passive tobacco exposure seem to increase breast cancer risk. These findings in combination with the high prevalences of tobacco smoke exposures, the increasing tobacco consumption among German youths, and the existance of undetected highly susceptible genotypic subgroups in the population emphasize the need for strong public health recommendations concerning a reduction of tobacco consumption.