IN-UTERO ORGANOCHLORINE EXPOSURE, GENE EXPRESSION OF AROMATASE, AND ABNORMAL PAP SMEARS

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Background and Aims: We have previously demonstrated that prenatal exposure to organochlorines is associated with gene expression of aromatase, an enzyme in estrogen synthesis. It is also known that aromatase is overexpressed in HPV positive cervical cancer cells. Estrogen activates HPV in cervical carcinogenesis. The objective of this study is to determine the association between prenatal exposure to organochlorines and abnormal Pap smear, mediated by altered gene expression of aromatase.
Methods: Female offspring of the Michigan Fisheater's Cohort (recruited 1973-1991) were contacted in 2001/2 and 2006/7. Interview variables included age and reproductive history. Leukocyte gene expression was determined and standardized with RNA Polymerase II. Generalized estimation equations and path-analyses were used to investigate the link between prenatal organochlorine exposure, gene expression, and Pap smear results.
Results: 139 women birthed by 93 mothers were identified. Of 134 women with complete data, 22 reported abnormal Pap smears. The average age at interview was 40 years (20.2 – 52.8) and of menarche, 13 years (11.0-16.0). Ninety-eight were premenopausal, 11 perimenopausal, and 24 postmenopausal.

Mean values of gene expression for *CYP19* were higher (p=0.03) in women with abnormal Pap smears and marginally different for *ESR1,* (p=0.09), which codes for ERα. No difference was found for 17-α-hydroxylase or *ESR2.* The path analysis showed no direct effect between prenatal organochlorine exposure and abnormal Pap smears, but a significant indirect effect via higher expression of *CYP19*.
Conclusions: These results demonstrate an association between abnormal Pap smears and the gene expression of *CYP1* that is not directly related to in-utero organochlorine exposure. This may reflect an indirect effect via gene expression, initiated earlier in life or a true negative effect. If the former is the case, the association between the gene expression of *CYP19* and abnormal Pap smears will need an alternative explanation.