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LETTER TO THE EDITOR

Cancer, genes and gender

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Susceptibility to some smoking-related cancers (lung, bladder, colon) is higher for women than for men; as yet unexplained observations. The commentary given by Haugen (1) in a recent issue of this journal underlines these notions with respect to lung cancer. Variations in genetic susceptibility factors were discussed, but some additions are at hand.

The association between N-acetyltransferase (NAT2) polymorphism and bladder cancer is well established; the risk may be higher in women than in men who smoked (2,3). Metabolizing identical substrates as NAT2, myeloperoxidase (MPO) is a candidate contributing to sex-related differences in cancer risk. MPO-generated oxidants are capable of oxidizing a wide variety of compounds, among these also products of tobacco smoke. Leukocytes are recruited in immune response and, therefore, reactive intermediates from xenobiotics generated by leukocyte metabolism may play a role in idiosyncratic drug reactions (4,5). Various drugs, but also arylamines and benzo[a]pyrene from tobacco smoke are converted to cytotoxic products. The degranulation of these cells and also their hyperactive state in the presence of chronic antigenic stimulation may transform environmental pre-carcinogens to highly reactive intermediates (6) as was shown for heterocyclic amine activation by MPO in fibroblasts and epithelial cells (7). Moreover, MPO provides one pathway for mutagenesis and cytotoxicity at sites of inflammation.

The –463 G/A polymorphism of the MPO gene promoter affects the risk of various diseases. Subjects bearing the A/G or A/A allele have a reduced risk to suffer from advanced lung cancer (8–10) and esophageal cancer (11). Likewise, this was also seen in coronary artery disease (12), Helicobacter pylori infections (13), in periodontitis (14) and neuro-degenerative disorders, i.e. Alzheimer’s disease (15) and multiple sclerosis (16). In all these studies, the allelic variant MPO-463A elicited a protective effect with nearly identical odds ratios in the range of 0.3–0.7, approximately. In some of these studies gender-specific results were presented showing the protective effect of the MPO A-allele only in females (14–16).

There must be a common link leading to this correspondence in the different clinical settings. Inflammation-related recruitment of neutrophil leukocytes into the affected tissue is most probably responsible for the different protective effects seen in the various studies mentioned. Exchange of an adenosine for a guanosine at position –463 in the 5'-untranslated region of the MPO gene leads to the loss of a transcription factor binding site. Reduced binding of transcription factor SP1 results in the diminished expression of MPO (17). The observed sex-specific differences suggest that binding of sex hormones may be affected by the loss of the MPO promoter binding motif. Possible interactions are known between the SP1 binding site and binding of the estrogen receptor to regulatory gene sequences (18). In vitro experiments demonstrated that the –463 G/A results in an estrogen receptor binding to the MPO A promoter, but not the MPO G promoter (19). This suggests that the –463 G/A base exchange affects the MPO expression differently in men and women. Potential estrogen responsive elements were also detected within the introns 7 and 9 of the MPO gene (20).

As a potential cause of MPO-induced tissue destruction in inflammatory diseases, it was reported that estrogen enhances MPO activity in human polymorphonuclear leukocytes (21). Reports on variations in MPO activities depending on estradiol levels during the menstrual cycle support this view (22) as well as the observation that hormone replacement restores the reduced neutrophil myeloperoxidase release and activity in menopausal women (23).

Elimination and/or toxification reactions of cigarette smoke products are subject to competing metabolic pathways including members of the cytochrome P450 family, NAT1 and NAT2, MPO and prostaglandin H synthase. Some of them may be regulated by hormonal response.

References

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