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RE "ASSOCIATIONS BETWEEN BREAST CANCER RISK AND THE CATALASE  
GENOTYPE, FRUIT AND VEGETABLE CONSUMPTION, AND SUPPLEMENT USE"

Rachel Nadif <sup>1</sup>, Steven R. Kleeberger <sup>2</sup> and Francine Kauffmann <sup>1</sup>

<sup>1</sup> INSERM U472-IFR69, Epidemiology and Biostatistics, Villejuif, France

<sup>2</sup> Laboratory of Respiratory Biology, NIEHS, Research Triangle Park, NC

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## RE “ASSOCIATIONS BETWEEN BREAST CANCER RISK AND THE CATALASE GENOTYPE, FRUIT AND VEGETABLE CONSUMPTION, AND SUPPLEMENT USE”

We read with interest the paper by Ahn et al. (1) on breast cancer in which they reported a protective role of catalase -262 CC genotype, enhanced by high fruit intake, a source of antioxidants. This result is of potential great importance as catalase is a primary defence against oxidative stress, which could play a role in a variety of diseases. They observed that the CC genotype was associated with higher catalase activity in 18 subjects, a result at variance with the lower protein level observed by Forsberg in 29 subjects (2) and concluded that larger genotype-phenotype association studies are required. We recently did such a study in a sample of 196 coal miners in France and have confirmed the highest red blood cell catalase activity in coal miners with *CAT* -262 CC genotype, miners with the TT genotype having a loss of activity of 31 percent (3). Our results extend those of Ahn et al. (1) with another method of measurement, and we also showed that individuals who were heterozygous for the T allele had intermediate activity.

Regarding gene by environment interactions, the study by Ahn et al. (1) and ours provide convergent results. In both studies the effect of factors previously found to be protective was enhanced only in subjects with the CC genotype (*i.e.* with genetically high catalase activity). In the Long Island Breast Cancer study project, significantly lower risk was observed among women with high fruit or/and vegetable intake, an environment rich in antioxidants, and this effect was enhanced in *CAT* -262 CC carriers. In our study, miners carrying the *NcoI* B1 allele in the lymphotoxin alpha gene (*i.e.* with low level of circulating pro-inflammatory cytokine (4)) have been found to be at lower risk of pneumoconiosis (5), considering disease prevalence and computed tomography (CT) score, a subclinical marker of the disease. After stratifying according to *CAT* -262 polymorphism, we observed that this effect was enhanced in *CAT* -262 CC carriers ( $p$  interaction =0.01 both for 4-year change in CT score and pneumoconiosis prevalence at the end of the follow-up). Regardless of the disease, both studies showed that the effects of other factors studied seems to be beneficial only in subjects with the *CAT* -262 CC genotype.

Among *CAT* -262 T carriers (*i.e.* with genetically low catalase activity), coal dust exposure, an environment rich in oxidants and the primary risk factor for pneumoconiosis, further decreased the catalase activity (3). Moreover, *CAT* -262 T carriers were less frequent in highly exposed miners than in others (OR=0.39 [0.20 – 0.78]), an observation which needs confirmation, but consistent with a healthy worker effect related to deleterious consequences of low catalase activity. From the data by Ahn et al. (1) apparently no association was observed between environment and genotype, but here the environment studied was a protective one.

It is possible that the -262 catalase polymorphism has an important role in numerous oxidant-related diseases and it has not been studied until now in large epidemiological surveys. The study by Ahn et al. (1), by investigating associations with the genotype controlling a relevant enzyme activity, presents methodological advantages which have been described as Mendelian randomization (6), as it may control for unmeasured confounders. Indeed, considering *CAT* -262 genotype or classes based on catalase activity as done previously (5) did not show the same interaction with the lymphotoxin alpha polymorphism. In conclusion, to better understand whether catalase has a pivotal role leading to heterogeneous etiology according to *CAT* -262 CC genotype in oxidant-related diseases, it is important to consider simultaneously the genotype and the enzymatic level, with potential oxidant and antioxidant environmental factors.

Rachel Nadif<sup>1</sup>, Steven R. Kleeberger<sup>2</sup> and Francine Kauffmann<sup>1</sup>

<sup>1</sup>INSERM U472-IFR69, Epidemiology and Biostatistics, Villejuif, France

<sup>2</sup>Laboratory of Respiratory Biology, NIEHS, Research Triangle Park, NC

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