

Correspondence

Extension of the "hygiene hypothesis" to the association of occupational endotoxin exposure with lower lung cancer risk

To the Editor:

The article by Liu¹ suggests that exposure to endotoxin can result in a lower incidence of atopic and asthma/allergy through an effect on the T_H1/T_H2 balance. This hypothesis is supported by other studies,^{2,3} though it remains controversial.³ The "hygiene hypothesis" suggests that those exposed to a very clean environment with few inflammagenic agents (such as endotoxin) remain shifted to T_H2, which regulates increased IgE, mucus production, eosinophilia, and mast cell growth.⁴ Those having higher exposure to environmental contaminants shift toward T_H1-mediated immunity with a protection against allergens.^{2,3} We suggest to the readers that the inflammation induced by endotoxin might have further benefits on disease risk as a result of actions on the immune system.

A number of publications (Table I) have reported a reduced risk for cancer, particularly lung cancer, in occupational populations exposed to dusts containing endotoxin, such as cotton dust and dust on farms.^{9,11}

For each of these studies the comparison group is the general population, and the risk estimates are never adjusted for smoking. However, in one cohort nested case-control study (G.M.; personal data), lung cancer risk decreased in dairy farmers by 19% for each increase of a unity in the number of cattle (odds ratio, 0.81; CI, 0.68-0.97) when the influence of age and smoking habits was controlled. Moreover, in subjects employed in the production of mutagenic and carcinogenic mustard gas in Japan between 1927 and 1945, a significant suppression

of cancer development in comparison with respect to untreated controls was noted in subjects treated with *Nocardia rubra* cell skeleton—which has effects comparable to those of endotoxin—after the elimination of the influence of smoking.¹²

The findings in these reports are supported by results from experimental studies¹³ and clinical trials using endotoxin.¹⁴ The latter report,¹⁴ a review of human and animal studies, shows that endotoxin increases the counts of cytotoxic T lymphocyte precursors, induces the secretion of various cytokines (such as TNF- α , IFN- γ , IL-1 β , and IL-6), and activates immune cells (including neutrophils, macrophages, and CD4 and CD8 T lymphocytes that infiltrate tumors).

It has been well established that endotoxin is an inflammagenic agent¹⁵ and that it is the likely cause of serious respiratory disease among those exposed to organic dusts.^{15,16} In addition to these effects caused by an inflammation, endotoxin might also be responsible for the reduced cancer rate through a stimulation of the immune system. This immunologic mechanism of protection against cancer in exposed populations has been suggested to be associated with immunomodulators, most likely through toll-like receptors.¹⁷⁻¹⁹ However, additional investigation is needed to elucidate the molecular mechanism.

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TABLE I. Epidemiologic studies on exposure to organic containing dust with endotoxin and lung cancer and other cancers

Author, year (reference)	Lung cancer		Other cancers	
	No. of cases	SMR	No. of cases	SMR
Cotton textile industry workers				
Enterline, 1965 (5)†	7	0.27*	48	0.72*
Henderson and Enterline, 1973 (6)†	20	0.55*	71	0.75*
Daum et al, 1975 (7)†				
Work <20 y	6	1.63	8	0.84
Work >20 y	6	0.67	17	0.67
Merchant and Ortmeier, 1981 (8)†				
Low exposure	15	1.01	32	0.84
High exposure	5	0.40*	13	0.41*
Dairy farmers, grain farmers				
Mastrangelo et al, 1996 (9)	23	0.49*	70	0.73*
Lange, 1988 (10)	43	0.61*	437	0.99

SMR, Standard mortality ratio.

* $P < .05$.

†Studies reviewed by Enterline (1985; reference 11).

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Are encasings effective in asthma caused by house dust mite allergens?

To the Editor:

Halken et al¹ report an effect of encasings in 47 children, measured as reduction in inhaled steroids. Reduction in medication usage is very susceptible to bias if the study is not perfectly blinded. It seems that the active and placebo encasings were not identical in appearance (the latter “resemble[d] the active treatment covers as much as possible”¹), and breakage of the blinding could therefore have occurred.

There is no description of the complicated randomization method, stratification after 4 factors. Was minimization used, and was the intended matching successful? It seems that the 2 groups were incomparable at baseline for the most important variable, asthma symptoms, inasmuch as the mean scores, on a scale of 0 to 3, were 3.33 and 1.62 for daytime symptoms. No measures of dispersion (such as SD) were provided, and the reader therefore cannot calculate the *P* value for this large difference. In a previous poster presentation, the authors reported scores of 3.07 and 1.90.² Why is there this discrepancy, and how can an average score exceed 3 when the scale only goes to 3? And what were the data for the other secondary variables—eg, peak flow—before and after treatment and for the variables used for the matching?

A recent, much larger placebo controlled trial, also of encasings, in 1150 adult patients failed to find a reduction in inhaled steroids after 12 months, either in all subjects or in the two thirds of the subjects who were allergic to mites.³ It therefore seems premature to conclude that encasings are useful. We have previously failed to show an effect of encasings in our systematic review of 29 trials of chemical and physical methods of reducing exposure to house dust mite antigens in the homes of mite-sensitive asthmatics, and we will update our review when the large trial⁴ is published in full.

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To the Editor:

As regards the comments by Gøtzsche and colleagues,¹ we are grateful for this opportunity to emphasize some points in our study.² We agree that the blinding is very important, and therefore we did our utmost to ensure a real double-blinding with respect to the production, distribution, and handling of the encasings during the study. Because the placebo encasings had to be made of a material that was different from that of the active encasings,