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LETTERS

Should we warn against night shifts to prevent breast cancer?

In Denmark, breast cancer has been recognised as an occupational disease since the International Agency for Research on Cancer (IARC) decided in 2007 that shift work involving circadian disruption is probably carcinogenic to humans.¹ Compensation has been given to 26 nurses, 12 nursing assistants, four physicians and 14 workers from other occupations who had worked night shifts for more than 20 years. This has caused public concern and prompted demands for setting limits for the duration of night shift work. We therefore reviewed exposure–response data for night shift work and breast cancer risk based on previously published epidemiological data.

We examined eight epidemiological studies which were recently reviewed.² We extracted information on risk of breast cancer in relation to duration of night shift work. One study that did not provide this information was excluded,³ and two studies published later were included.^{4–5} We conducted a dose–response meta-analysis based on weighed least squares random effects regression models.⁶ The natural logarithms of the reported risk estimates were assigned to the midpoints of the lower and upper boundaries of the corresponding duration categories.

The data showed large heterogeneity across the individual studies and no indication of an overall increasing risk of breast cancer by increasing years of night shift work (OR 1.02, 95% CI 0.92 to 1.13; figure 1). Analyses that dichotomised night shift work by successively increasing duration did not reveal any thresholds.

These limited epidemiological data do not indicate an exposure–response relationship between night shift work and breast cancer. Furthermore, the data do not provide empirical arguments for the 20 years' criterion applied for compensation for breast cancer in Denmark. No threshold level that could guide the regulation of night shift work is indicated. Therefore, warnings against long-term night shift work to prevent breast cancer are not evidence based. On the other hand, effects on sleep, comfort and social life are sound reasons to limit work at night.

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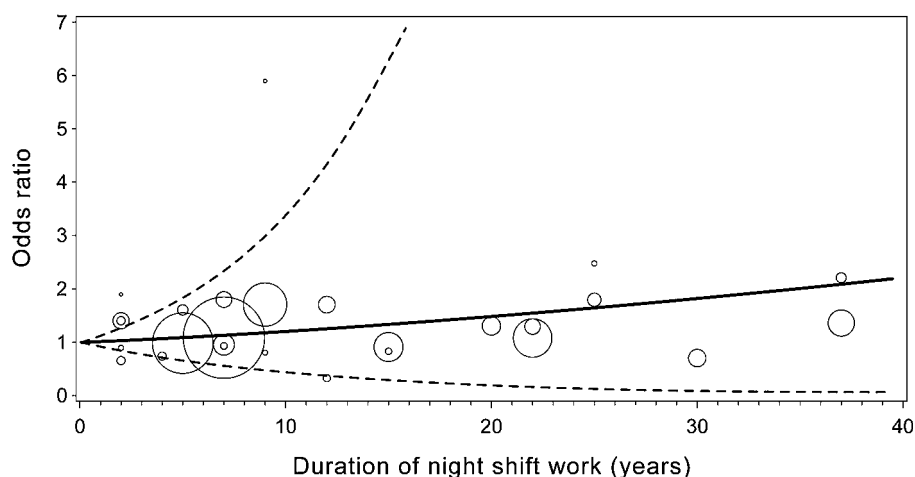


Figure 1 Odds ratio of breast cancer by duration of night shift work: bubble plot of results from nine epidemiological studies, where the area of each circle is proportional to the precision of the risk estimate. The meta-regression OR function with a 95% CI is also plotted.

Competing interests None.

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Occupational allergic rhinoconjunctivitis and bronchial asthma induced by *Plukenetia volubilis* seeds

Plukenetia volubilis, *Euphorbiaceae* (Sacha Inchi) is a plant from the Peruvian Amazon whose seeds are used in the cosmetic industry for their oil and protein content.^{1,2}

P. volubilis has not been previously related to allergy. However, allergens have been

described from other *Euphorbiaceae* plants (<http://www.allergen.org/>): *Hevea brasiliensis* (13 allergens), *Mercurialis annua* (Mer a 1) and *Ricinus communis* (Ric c 1). Cross-reactivity among these species has been reported.³

A 40-year-old woman developed rhinoconjunctivitis and bronchial asthma related to exposure to *P. volubilis* seeds in a cosmetic company. She was in charge of crushing the seeds to obtain the powder to extract the oil, had constant rhinoconjunctivitis and had had episodes of coughing, dyspnea and

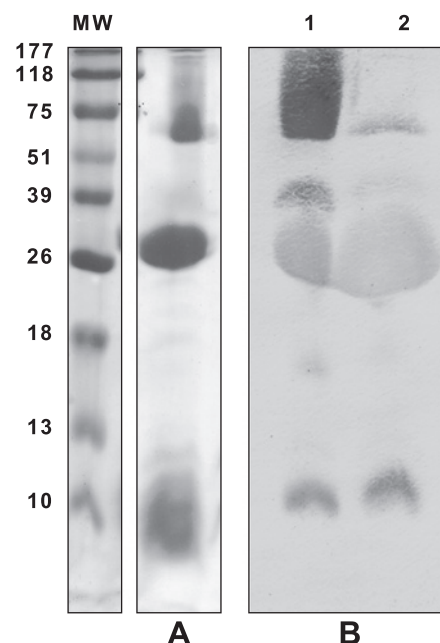


Figure 1 (A) Protein separation by SDS-PAGE from *Plukenetia volubilis* seed extract. (B) IgE-immunoblotting performed with the patient's serum. Lanes: (1) *P. volubilis* seed extract; (2) extract reduced with 5% 2-mercaptoethanol at 100°C for 5 min. MW, molecular weight markers.

wheezing for 2 years. The symptoms disappeared on holidays and at weekends, suggesting an occupational exposure.

The patient had a normal respiratory function test (FEV₁) of 3.45 litres (98% predicted). The bronchodilator test was negative.

Common pneumoallergens were investigated by skin prick tests and the CAP system (Phadia, Uppsala, Sweden), resulting positive cat and dog epithelia. The CAPs to latex from *H brasiliensis* and to *R communis* seeds were both negative, ruling out cross-reactivity in the patient between these species and *Plukenetia*.

Prick-to-prick test with *P volubilis* seed extract (crushed seeds in saline solution 10 mg/ml) was positive (8×7 mm). Furthermore, opening of the extract bottle elicited an immediate response with rhinitis, conjunctivitis, cough and dyspnea (24% decrease in FEV₁). The patient required treatment with nebulised salbutamol and methyl-prednisolone.

To identify the allergens involved, crushed seeds (10 g) were defatted twice with acetone (1:10 (wt/vol) 4°C/1 h) and ethanol/ether (1:3 (vol/vol) 4°C/1 h). The defatted material was extracted with PBS (4°C/2 h). After centrifugation (4500 g/30 min), the supernatant was dialysed and freeze-dried. The extract (15 µg of protein) was analysed by SDS-PAGE and IgE-immunoblotting with the patient's serum as described.⁴

SDS-PAGE revealed bands of apparent molecular weights around 8, 10, 27 and 73 kDa, and weaker bands of 12, 15, 17 and 39 kDa (figure 1A). The patient's serum detected allergens around 10, 15, 27 and 39 kDa and a smear at 73–177 kDa. Reduction (5% 2-mercaptoethanol, 100°C/5 min) did not affect the allergenicity of the 10, 27 and 39 kDa proteins, although the weakly recognised 15 kDa allergen disappeared and a 73 kDa allergen was observed instead of the smear.

The patient's serum detected an allergen around 10 kDa from the *Plukenetia* seed extract, a molecular weight similar to that of Ric c 1, a 2S albumin.⁵ Nevertheless, the allergenicity of the *Plukenetia* allergen was not affected after reduction, suggesting that it did not correspond to 2S albumin.

Sensitisation to rubber latex among healthcare workers and occupational cases of castor bean allergy have been reported.⁶ However, to our knowledge, this is the first reported case of occupational allergy induced by *P volubilis* seeds. Thus, surveillance of the occupational exposure to *P volubilis* should be performed to avoid further cases of sensitisation to this allergenic seed.

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Occupational asthma due to 5-aminosalicylic acid

5-Aminosalicylic acid (5-ASA) is an anti-inflammatory drug with a structural resemblance to phenacetin and is widely used to treat inflammatory bowel diseases. 5-ASA is the active constituent of sulphasalazine and sulphapyridine is its transport molecule. Some studies suggest that the serious adverse effects of the drug are in many cases due to sulphapyridine; however, at least in some patients, the adverse effects of sulphasalazine are attributable to 5-ASA itself.^{1 2} Pharmaceutical development has concentrated on delivering 5-ASA to the mucosa of the small intestine and colon using other inert carriers such as mesalazine. Blood dyscrasias, hepatitis, pancreatitis, pericarditis, pneumonitis and serious skin reactions have been reported in patients treated with sulphasalazine. Allergy to ASA and other salicylates, such as aspirin, has been reported.³ We report a case of occupational asthma due to 5-ASA.

A 56-year-old man complained of cough, dyspnea and wheezing 1 month after beginning work manufacturing a drug containing 5-ASA, in spite of taking measures to protect his skin and respiratory system. Symptoms typically appeared 6 h after the start of shifts. Symptoms worsened with the passing of time. The patient was treated with salbutamol as needed. For the last 30 years he has worked for a pharmaceutical company manufacturing various drugs. The man was diagnosed with occupational asthma caused by amoxicillin 29 years ago and with nasal polyposis 7 years ago. He currently works in the manufacture of levofloxacin and tolerates oral amoxicillin and ibuprofen. The patient was evaluated 6 months after he had discontinued his contact with 5-ASA. Physical examination, blood tests and spirometry results were normal. Skin prick tests with common inhalants showed positive results to grass pollen, with a negative reaction to 5-ASA (10 mg/ml). Methacholine PC₂₀ was >16 mg/ml, fraction of exhaled nitric oxide (FE_{NO}) level was 32 ppb, and sputum induced by hypertonic saline inhalation and processed as previously described,⁴ showed no eosinophils. After signed informed consent was provided by the patient, an exposure challenge was carried out with a placebo (lactose as sham exposure) in a 7 m³ chamber for 30 min. The results showed no changes in FEV₁ over 24 h, as measured hourly with a computerised flow metre (Amos, Jaeger, Germany) while respecting sleep time. On visit 2, the patient was exposed to 5-ASA (5% in lactose) in the chamber at a mean concentration of 2.65 mg/m³ for a total of 30 min. A late response, with a maximum fall in FEV₁ of 16%, was elicited 9 h after the challenge. At 24 h after the challenge, methacholine PC₂₀ level was 10 mg/ml, FE_{NO} level was 53 ppb and induced sputum showed 65% eosinophils.

The above results demonstrate that 5-ASA inhalation was able to induce an eosinophilic asthmatic reaction and, while the underlying mechanism causing this event is still unknown, it appears to be similar to that of other low-molecular-weight agents causing immunologic occupational asthma. To our knowledge, this is the first report of occupational asthma due to 5-aminosalicylic acid.

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