Title
Reply to Comment on: 'Possible pro-carcinogenic association of endotoxin on lung cancer among Shanghai women textile workers'

Journal
British Journal of Cancer, 112(11)

ISSN
0007-0920

Authors
Checkoway, H
Lundin, JI
Costello, S
et al.

Publication Date
2015-05-01

DOI
10.1038/bjc.2014.584

Peer reviewed

independent of oestrogen pathways, such as metabolic dysfunction (Gangwisch *et al*, 2007) and chronic inflammation (Irwin *et al*, 2006).

Again, we thank Yang *et al* for this letter and are glad that more studies, such as the population-based case–control study in Jiujiang city mentioned by Yang *et al*, are using objective measures along with questionnaires to better assess both the quantity and quality of sleep in relation to breast cancer risk and other health outcomes.

REFERENCES

Blask DE (2009) Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev* **13**(4): 257–264.

Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG *et al.* (2007) Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Sleep* **30**(12): 1667–1673.

Girschik J, Heyworth J, Fritschi L (2013) Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. *Am J Epidemiol* **177**(4): 316–327.

Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S (2006) Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med* **166**(16): 1756–1762.

Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ (2008) Self-reported and measured sleep duration: how similar are they? *Epidemiology* **19**(6): 838–845.

Vogtmann E, Levitan EB, Hale L, Shikany JM, Shah NA, Endeshaw Y *et al.* (2013) Association between sleep and breast cancer incidence among postmenopausal women in the women's health initiative. *Sleep* **36**(10): 1437–1444.

Yang W-S, Wang X, Deng Q, Zhao H, Fan W-Y (2015) Sleep duration and breast cancer risk in the breast cancer detection demonstration project follow-up cohort: true associations or bias? *Br J Cancer* **112**(11): 1838–1839.

*Correspondence: Dr Q Xiao; E-mail: qian.xiao@nih.gov
Published online 21 April 2015

BJC

British Journal of Cancer (2015) 112, 1840 | doi: 10.1038/bjc.2014.583

Comment on 'Possible pro-carcinogenic association of endotoxin on lung cancer among Shanghai women textile workers'

R Rylander*[,1] and R Jacobs[2]

[1]*BioFact Environmental Health Research Center, Lerum, Sweden and* [2]*Environmental and Occupational Health Sciences, School of Public Health and Information Sciences, University of Louisville, Louisville, KY, USA*

Sir,

In a recent article in this Journal, Checkoway *et al* (2014) suggest that the exposure to endotoxin in industrial environments is associated with an increase in the risk of lung cancer.

A number of studies over the past 50 years has demonstrated a decreased risk in different environments involving a high exposure to endotoxin such as cotton handling and farming (Rylander, 1992; Maestrangelo *et al*, 2005; Lenters *et al*, 2010). Plausible cellular mechanisms for this defence have been discussed. In the data now presented there are no significant differences in risk—all are within the 95% confidence limit—and no significance for trend in relation to exposure duration. The only observation, thoroughly discussed, is a small, non-significant increase in risk in a subgroup. It is difficult to understand how such data can be used as a support to challenge a previously well-established relationship.

More serious is the lack of control of possible confounding factors. It is well known that indoor air pollution from cooking fuels is a risk factor for lung cancer. Such exposures change over the years and are closely related to socio-economic factors. The problem is discussed but in the absence of data the discussion remains speculative. Diet modulates the risk of lung cancer but is not discussed (Seow *et al*, 2002; Rylander and Axelsson, 2006). Finally, possible changes in endotoxin exposure over the years are not dealt with. Also in China, work hygiene standards have improved over the years since the measurements were made and could result in a change of exposure to endotoxin.

In view of the above, a correct conclusion from the material presented is that 'no relation between endotoxin exposure and lung cancer risk could be detected'.

REFERENCES

Checkoway H, Lundin JI, Costello S, Ray R, Li W, Eisen EA, Astrakianakis G, Seixas N, Applebaum K, Gao DL, Thomas DB (2014) Possible pro-carcinogenic association of endotoxin on lung cancer among Shanghai women textile workers. *Br J Cancer* **111**: 603–607.

Lenters V, Basinas I, Beane-Freeman I, Boffetta P, Checkoway H, Coggon D, Portengen L, Sim M, Wouters IM, Heederik D, Vermeulen R (2010) Endotoxin exposure and lung cancer risk: a systematic review and meta-analysis of the published literature on agriculture and cotton textile workers. *Cancer Causes Control* **21**: 523–555.

Maestrangelo G, Grange J, Fadda E, Fedeli U, Buja A, Lange JH (2005) Lung cancer risk effect of dairy farming and the consequence of removing occupational exposure. *Am J Epidemiol* **161**: 1037–1046.

Rylander R (1992) Environmental exposures with decreased risk for lung cancer? *Int J Epidemiol* **19**: S67–S71.

Rylander R, Axelsson G (2006) Lung cancer risk in relation to vegetable and fruit consumption and smoking. *Int J Cancer* **118**: 739–743.

Seow A, Poh WT, The M, Eng P, Wang YT, Tan WC, Chia KS, Yu M, Lee HP (2002) Diet, reproductive factors, and lung cancer risk among Chinese women in Singapore: evidence for a protective effect of soy in non-smokers. *Int J Cancer* **97**: 365–371.

*Correspondence: Professor R Rylander; E-mail: envhealth@biofact.se
Published online 20 November 2014

BJC

British Journal of Cancer (2015) 112, 1840–1841 | doi: 10.1038/bjc.2014.584

Reply to Comment on: 'Possible pro-carcinogenic association of endotoxin on lung cancer among Shanghai women textile workers'

H Checkoway*[,1], J I Lundin[2], S Costello[3], R M Ray[4], W Li[4], E A Eisen[5], G Astrakianakis[6], K Applebaum[7], D L Gao[8] and D B Thomas[4]

[1]*Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA 92093, USA;* [2]*Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA;* [3]*Department of Environmental Health Sciences, University of California, Berkeley, Berkeley, CA, USA;* [4]*Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA;* [5]*Department of Environmental Health Sciences, University of California, Berkeley, Berkeley, CA, USA;* [6]*School of Population and Public Health, University of British Columbia, Vancouver, BC V6T1Z4, Canada;* [7]*Department of Environmental and Occupational Health, George Washington University, Washington, DC 20052, USA and* [8]*Zhong Shan Hospital Cancer Center, Shanghai 2000030, China*

Sir,

We appreciate the thoughtful comments by Rylander and Jacobs (2015) on our paper (Checkoway *et al*, 2014). The absence of an inverse exposure–response relation for endotoxin and lung cancer in the extended follow-up was somewhat unexpected in view of the reported consistent findings from numerous prior studies, including our initial follow-up of the

Shanghai textile worker cohort (Astrakianakis *et al*, 2007). Although neither the modest excess relative risks observed nor the exposure–response trend for exposures >15 years since first exposure (Table 3) were statistically significant, the findings are somewhat suggestive of a possible late pro-carcinogenic effect. We do not believe that our observations on endotoxin exposure and lung cancer risk necessarily challenge a well-established association. Instead, we would argue that the exposure–response association may change over time owing to complex, yet poorly understood, underlying mechanisms. We are also not the first to report that an inverse association between endotoxin and lung cancer risk may be time varying, diminishing over time (Mastrangelo *et al*, 2005).

We have acknowledged the absence of data on risk factors other than active smoking, such as indoor air pollution from cooking fuels and diet. However, it is highly unlikely that either indoor air pollution or diet was correlated with endotoxin exposure in this cohort, and thus were probably not important confounders. Socio-economic status was relatively homogenous in the cohort, and also was unlikely to have been a confounder. Our exposure assessment for endotoxin (Astrakianakis *et al*, 2006) did take into account temporal changes in exposure levels during the cohort's relevant work experience, to the extent that available historical data permitted. Endotoxin is a highly variable exposure, and as we noted in the paper, some exposure misclassification was inevitable.

We encourage analyses that consider temporal patterns of association in other endotoxin-exposed study populations, which can provide valuable insights into disease aetiology and pathogenesis.

REFERENCES

Astrakianakis G, Seixas NS, Camp JE, Christiani DC, Feng Z, Thomas DB, Checkoway H (2006) Modeling, estimation and validation of cotton dust and endotoxin exposures in Chinese textile operations. *Ann Occup Hyg* **50**(6): 573–582.

Astrakianakis G, Seixas NS, Ray R, Camp JE, Gao DL, Feng Z, Li W, Wernli KJ, Fitzgibbons ED, Thomas DB, Checkoway H (2007) Lung cancer risk among female textile workers exposed to endotoxin. *J Natl Cancer Inst* **99**(5): 357–364.

Checkoway H, Lundin JI, Costello S, Ray R, Li W, Eisen EA, Astrakinakis G, Seixas N, Applebaum K, Gao DL, Thomas DB (2014) Possible Pro-carcinogenic association of endotoxin on lung cancer among Shanghai women textile workers. *Brit J Cancer* **111**(3): 603–607.

Mastrangelo G, Grange JM, Fadda E, Fedeli U, Buja A, Lange JH (2005) Lung cancer risk: effect of dairy farming and the consequence of removing that occupational exposure. *Am J Epidemiol* **161**(11): 1037–1046.

Rylander R, Jacobs R (2015) Comment on 'Possible pro-carcinogenic association of endotoxin on lung cancer among Shanghai women textile workers'. *Br J Cancer* **112**(11): 1840.

*Correspondence: Professor H Checkoway; E-mail: hcheckoway@ucsd.edu
Published online 20 November 2014

BJC

British Journal of Cancer (2015) 112, 1841–1842 | doi: 10.1038/bjc.2015.106

Response to 'Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France'

C R Muirhead*,[1]

[1]Institute of Health & Society, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne, NE2 4AX, UK

Sir,

The recent paper by Journy *et al* (2015) addresses an important issue regarding the interpretation of epidemiological studies of CT scans and cancer risk. It has been suggested that raised risks reported in the studies in Northern England (Pearce *et al*, 2012) and Australia (Mathews *et al*, 2013) might reflect the early symptoms of undetected cancer, or of factors that predispose to cancer and which are the indications for the CT scans, rather than an effect of the CT scans *per se* (Walsh *et al*, 2014). The study of Journy *et al*–based on a cohort of children who received CT scans at 23 radiology departments in France–benefits from the availability of information on predisposing factors for cancer. However, I have concerns that their findings could be misinterpreted.

Table 1 here combines the results from Table 5 and Supplementary Table 6 from the study by Journy *et al*. The authors have highlighted that – for each cancer type – the estimate of the excess relative risk (ERR) per 1 mGy cumulative organ dose is lower with adjustment for predisposing factors than without such an adjustment. At face value, this might suggest confounding by indication, reflecting higher cancer risk and potentially higher radiation doses from CT scanning among children with predisposing factors compared with children without such factors. However, Table 1 here also shows that – for each cancer type – the ERR among children without predisposing factors is at least as large as the unadjusted value for the cohort overall, whereas the ERR among children with predisposing factors is close to zero. This suggests that the difference between the unadjusted and adjusted values principally reflects modification of the ERR by predisposing factors, rather than confounding.

It is unclear from the study by Journy *et al* to what population the adjusted ERR estimates apply. Looking at Table 1, the adjusted estimates appear to be similar to a weighted average of the ERR estimates for those either with or without a predisposing factor, with weighting based on the numbers of cancer cases in each group. This would suggest that the adjusted estimates reflect the prevalence of predisposing factors among those children who developed cancer. However, from a public health perspective, it is more relevant to consider the prevalence of predisposing factors in the general population, rather than in the selected population

Table 1. Number of cases and associated risks of primary tumours of the CNS, leukaemia, and lymphoma

	CNS cancer				Leukaemia				Lymphoma			
	Cases	IR	ERR	95% CI[a]	Cases	IR	ERR	95% CI	Cases	IR	ERR	95% CI
All children	22	9.4			17	7.3			19	8.1		
Unadjusted for predisposing factors[b]			0.022	−0.016, 0.061			0.057	−0.079; 0.193			0.018	−0.068; 0.104
Adjusted for predisposing factors			0.012	−0.013, 0.037			0.047[c]	−0.065; 0.159			0.008	−0.057; 0.073
Children without a predisposing factor	15	6.4	0.028	n.a.	12	5.2	0.187	n.a.	12	5.2	0.025	n.a.
Children with a predisposing factor	7	565.9	−0.005	n.a.	5	128.0	−0.012	n.a.	7	160.3	−0.005	n.a.

Abbreviations: CNS = central nervous system; CI = confidence interval; ERR = excess relative risk; IR = incidence rate; n.a. = not available. The table provides the IR per 100 000 person-years, ERR related to cumulative organ dose (in mGy) from CT scans, for all children (without and with adjustment for predisposing factors), and separately for children with and without predisposing factors, with a 2-year exclusion period (based on Journy *et al*, 2015).

[a]Wald-based CI for the ERR.

[b]Factors predisposing specifically to cancer at the site specified.

[c]Listed as 0.045 in Supplementary Table 6 of Journy *et al*.