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Letters to the Editor

Maternal cured meat consumption during pregnancy and risk of paediatric brain tumour in offspring: potentially harmful levels of intake

Sir,

The recent article by Pogoda and Preston-Martin suggests that high intake of nitrite from cured meats by women during pregnancy increases the risk of paediatric brain tumours in their children between birth and 19 years of age[1]. This study is a re-analysis of previously published data[2] that also found a significant protective effect of daily use of prenatal vitamins throughout pregnancy; also implicated as increasing risk were low consumption of fruit and vegetables and low intake of vitamin C. Cases were disproportionately from households with lower socio-economic status where exposure to a variety of chemicals may have been higher. In addition, there remains a number of open questions not resolved by this research.

The brain tumours analysed are astrocytomas, medulloblastomas, gliomas and seven rarer tumour types. Assuming nitrite were a carcinogen, it is not likely that all cells of the brain would respond similarly just as only certain types of lung cancer are induced by exposure to cigarette smoke or asbestos. The age of patients is problematic in the recent analysis. Bunin *et al.*[3] restricted analysis to the first five years of life, reasoning that if maternal diet mattered, it might be manifested earlier in childhood as opposed to adolescence. Not only might diet in later childhood affect risk of developing a brain tumour, but recall of diet from 15 years earlier is almost certainly less accurate than, and influenced by, recall of diet in the recent past.

Major sources of nitrite and nitrate were ignored in the analysis. Twenty per cent of nitrate, which comes mostly from vegetables, is converted to nitrite endogenously. Smoking status, a significant source of nitrosamines, of the mothers was ignored. Preston-Martin recently published another study[4] linking exposure to well water only in certain geographic areas as a risk factor for paediatric brain cancers. It is known that wells can be contaminated with a wide variety of natural and synthetic toxins.

Lubin *et al.*[5] found no increase in relative risk for nitrite intake during gestation or childhood. They faulted other studies for making no adjustments for energy intake and differences in age of cases. They pointed out that recall bias and poor recall are common to all retrospective studies of gestational factors and disease, and that they may be insurmountable for dietary studies. This position was also expressed by Blot *et al.*[6], who suggested a causal association between cured meat intake and brain tumours cannot be concluded and that additional case–control studies are not likely to help nor will meta-analyses because of methodological shortcomings. In adults, adjustment for energy intake greatly attenuated apparent increased risk for adult glioma and nitrite-containing meat[7]; in a study population ranging from one to 18 years this issue is critical.

Perhaps the most serious shortcoming in the analysis is that data presented for increased nitrite content of hot dogs in 1990 showed a sharp rise to 47 parts per million (ppm), in contrast to all other cured meats, based on the authors' reference 22, the only study cited from the 1990s. This was based on frankfurters made from Alaskan pollock, a fish product that is atypical. Analysis of 53 samples of hot dogs made from beef and pork showed average residual nitrite[8] of 8 ppm. Over the last 30 years, the meat processing industry has decreased residual nitrite by using less nitrite and by adding reducing agents.

While the hypothesis linking nitrite with brain tumours is plausible, it appears that the data are not conclusive nor does the present study add to our knowledge of this issue.

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Sir,

Most of Dr Klurfeld's concerns relate to our finding of increased brain tumour risk in offspring of mothers with relatively high consumption levels of nitrite from cured meats during their pregnancies. We published this finding in 1996[1] and many of the issues raised by Dr Klurfeld were addressed in that paper. The paper recently published in this journal[2] was not intended to be a republication of our original finding, nor was it a re-analysis of the original finding. Rather, it was an attempt to quantify, for the first time (to our knowledge), intake levels that might be potentially harmful. Nonetheless, we shall respond to Dr Klurfeld's comments.

Our cases were of somewhat lower socio-economic status (SES) than our controls; however, controlling for SES analytically had no effect on risk estimates and dose–response was observed in both lower- and upper-SES subgroups. Mother's smoking status was ignored because it is not an established risk factor for paediatric brain tumour and therefore cannot be considered a confounder of any other disease–risk factor relationship. In our case–control study in particular, mother's smoking status was not related to disease[3].

We agree that recall of distant exposure is a challenging epidemiological problem in any retrospective study that relies on recall. That we observed increased risk for both older and younger cases, as well as for all histological tumour types, might suggest that differential recall error biased our results. While we acknowledge that this cannot be ruled out, we note that we did not observe increased risk for exposures typically associated with harm to foetuses: alcohol consumption and, as noted above, smoking. On the other hand, if non-differential recall error occurred, it is highly unlikely that it would have created a false positive dose–response.

In our original paper, we analysed nitrite from vegetables and found no relationship, possibly because vegetables also contain high levels of nitrosation-inhibiting vitamins. In fact, we found that risk associated with cured meat consumption was substantially reduced among mothers who used vitamin supplements. Some vegetables are major sources of nitrate, which is reduced to nitrite in the saliva and enters the gut as a highly diluted nitrite solution[4]. However, much higher concentrations of nitrite in the stomach result from the ingestion of foods cured with sodium nitrite. Such highly concentrated nitrite reacts more rapidly and is more likely to lead to endogenous formation of *N*-nitroso compounds (NOCs) than the nitrite solution that results from the ingestion of nitrate.

Whether or not to control for total energy intake in any analysis of dietary risk factors should be thoughtfully considered in terms of biological significance. By no means should total energy intake always be controlled. If controlled in our analysis, the implication would be that total energy intake by mothers during pregnancy is somehow related to increased brain tumour risk in their offspring and is therefore a confounder. In our data, total energy intake was unrelated to brain tumour risk. Lubin *et al.*, whom Dr Klurfeld cites, analysed maternal cured meat consumption as a risk factor for paediatric brain tumour and controlled for total energy intake, despite concluding that total energy was unrelated to risk[5]. If total energy is treated as a confounder when in fact it is not, overmatching can occur, which produces biased risk estimates. It seems quite biologically feasible that absolute amounts of nitrite consumption by mothers during pregnancy are more relevant to foetal exposure than are relative amounts and that adjusting for total energy intake might therefore mask increased risk to offspring.

Dr Klurfeld correctly pointed out that we used only one reference from the 1990s for hot dogs and that this particular paper was about an atypical fish-product hot dog[6]. However, this survey also included nitrite levels for all-meat hot dogs, and we included these data points in our analysis. Further, Table 1 in our paper shows medians and midspreads of nitrite levels by 5-year intervals of our literature search and suggests an upward trend in hot dog nitrite levels over the time period we covered.

Dr Klurfeld cited a reference from 1997 showing much lower hot dog nitrite levels than we reported[7]. As stated in our paper, our target time period was 1965 to 1991, the years of pregnancies of mothers in our study. It is not surprising that a survey published in 1997 resulted in substantially lower nitrite levels. In fact, our concluding remark in our paper is that future studies of highly exposed subjects seem unlikely 'given the decline in nitrite levels that has occurred in cured meats over past decades'. It is for this reason that we concur with Blot *et al.*[8], who, as Dr Klurfeld noted, suggested that additional case–control studies are not likely to confirm an association between maternal nitrite consumption and paediatric brain tumour risk. We strongly disagree with Dr Klurfeld that our analysis does not add to the current knowledge of this issue, however. The decades covered by our study, the 1960s to the 1980s, provided a very unique opportunity to study highly exposed subjects. We are unaware of any other publication that quantified the

amount of nitrite consumption likely to result in increased risk of brain tumour.

Further, there are many environmental sources of NOC exposure. That residual nitrite levels in cured meats have been substantially reduced by meat manufacturers far from implies that NOCs have been eradicated.

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