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Tobacco Industry's dirty tricks continue

The tobacco industry is still striving to challenge the science linking smoking to adverse health effects, say US researchers. Despite its claims to be working with the public health community, ''the industry has not changed its practice'', they say (*Lancet 2005, online http://image.thelancet.com/extras/03art3495web.pdf.*)

The researchers, from University of California, San Francisco, USA, call on authors, editors, and users of scientific literature ''to be vigilant in demanding and maintaining rigorous standards for disclosing and evaluating potential conflicts of interest''.

They examined the tobacco industry's response to research published in 1996, which demonstrated that benzo[a]pyrene, a carcinogen present in tobacco smoke produced patterned in-vitro mutagenic effects on the tumour suppressor gene *p53* (*Denissenko et al., Science* 1996, **274**, 430–32). The authors concluded that the study ''provides a direct link between a defined cigarette smoke carcinogen and human cancer mutations''.

Documents made public as a result of litigation in the States revealed that executives and scientists at the highest levels of the tobacco industry anticipated and carefully monitored *p53* research, according to the *Lancet* article. Tobacco companies supported scientific studies which appeared to cast doubt on the link between *p53* damage and BDPE, a metabolite of benzo[a]pyrene. Authors of the research did not clearly disclose their links with the tobacco industry. It was published in a peer-reviewed journal whose editor had longstanding, undisclosed ties to the tobacco industry.

Later research from International Agency for Research on Cancer (IARC) used human lung tumours and confirmed Denissenko's findings (*Environ Health Perspect* 1998, **106**, 385–91). It was subject to similar challenges from the industry.

''Tobacco industry responses to research linking smoking to carcinogenic *p53* mutations mirror prior industry efforts to challenge the science linking smoking and lung cancer'', say the authors of the *Lancet* report.

''THE INDUSTRY MUST DEMONSTRATE TRUE SOCIAL RESPONSIBILITY''

The Uniform Requirements issued by the International Committee of Medical Journal Editors (ICMJE) specify that authors of all submitted manuscripts ''are responsible for recognising and disclosing financial and other conflicts of interest that might bias their work''. Editors who make final decisions about manuscripts ''should have no personal financial involvement in any of the issues they might judge''. However, the Requirements are guidelines and journals are not obliged to comply with them.

Tobacco companies now claim to be working with the public health community ''to support a single, consistent public health message on the role played by cigarette smoking in the development of disease in smokers''. The authors of the *Lancet* report conclude, ''Their multifaceted response to p53 research as recently as 2001, suggests that the industry has not changed its practice''.

Commenting on the report, Dr. Peter Boyle, director of IARC, said, ''The use of consultants, to publish purchased critiques of scientific research appears to remain one of the key strategic approaches of the tobacco industry''.

''Their strategy of infiltrating the scientific community to undermine the normal process of peer review and publication is distressing for the scientists whose work is targeted. It is also damaging for outstanding journals and academic institutions whose record with respect to tobacco research might appear to be blurred by the actions of a few individuals who maintained undisclosed tobacco industry ties.

''This industry needs to demonstrate true corporate social responsibility. Until then, the public health community can have no confidence in the actions of the tobacco industry, and academic institutions should refuse any involvement with them, no matter how loudly the industry claims that they will not interfere in the research''.

Bevacizumab approved in Europe

Roche has announced that its anti-angiogenesis agent, bevacizumab (Avastin) has been approved in the EU for use in patients with previously untreated metastatic colorectal cancer. The company says the drug will be accessible to physicians early this year.

The drug is now approved for the first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan.

The European Commission's approval was based on a Phase III study (*New Eng Jnl Med* 2004, **350**(23), 2335–342) which found that the addition of bevacizumab to chemotherapy increased survival and time to disease progression.

Roche and Genentech are exploring the use of the drug in the adjuvant setting and in other cancers, including non-small cell lung cancer, pancreatic cancer, breast cancer and renal cell carcinoma.

EJC News is compiled by:
Helen Saul
Tel: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.com

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Surgery 'may kick-start the growth of metastases'

A radical new model to explain the natural history of breast cancer suggests that the act of surgery could accelerate the clinical appearance of metastatic disease. The model, explained at length in this issue of *EJC*, (2005, **41**, 508–515) is proposed by a group led by Professor Michael Baum (Portland Hospital, London, UK).

Development of the model was prompted by the observation that the rate of relapse following surgery is non-linear, and peaks sharply 18 months after treatment. ''Some signal, perhaps the act of surgery or other adverse life-event stimulates [micrometastases] into fast growth'', they write.

The authors suggest that micrometastases may lie dormant while factors inhibiting angiogenesis dominate locally. If stimulating factors are increased or inhibiting factors reduced, the dormant condition will not be maintained. The first peak in the hazard for relapse is too sharp to be the result of steady transitions from single cells to avascular micrometastases. ''Some breaking of dormancy had to occur at surgery to explain the first peak'', they write.

Anti-angiogenic therapies, given pre-operatively, could be a therapeutic consequence of the model, so that at the time of surgery the system is primed to protect against sudden flooding with angiogenic signals. ''Indeed, some of the success attributed to adjuvant tamoxifen or chemotherapy might be a result of their anti-angiogenic potential rather than cytostatic/cytocidal effects'', the authors suggest.

''ANTI-ANGIOGENIC DRUGS COULD BE GIVEN PRE-OPERATIVELY''

In an accompanying editorial, Professor Samuel Hellman (University of Chicago, USA), says that the paper ''serves well to make us reconsider accepted paradigms''. The suggestion that the increased hazard of relapse 2 years after surgery could be due to the release from inhibitors produced by the primary, or because of some stimulation, is ''an interesting notion. This needs much more study'', he writes.

Randomised trials and meta-analyses of adjuvant breast cancer treatment could inform and enrich this observation, Professor Hellman said: ''These should be used to verify the observation and, if it is confirmed, to shed light on its cause with particular attention to the hypothesis that it is surgery that is the cause of the transient increase in the recurrences seen''.

Value of 'Excellence' Designation

Cancer surgery performed at a medical centre designated by the US' National Cancer Institute (NCI) as a ''Center of Excellence'' is associated with less perioperative mortality than if performed at a high-volume surgical centre. However, 5 year survival rates were similar.

Researchers from University of Michigan Medical School reviewed data on 63,860 patients undergoing cancer surgery. Results from the 51 NCI cancer centres were compared to those from 51 control cancer centres with the highest volumes for each procedure (*CANCER 2005 102*).

Perioperative mortality was significantly lower at the NCI centres for 4 of 6 procedures: colectomy; pulmonary resection; gastrectomy; and oesophagectomy. No significant difference in mortality was observed for cystectomy or pancreatic resection. Among the patients who survived surgery, there was no significant difference in 5 year survival.

In 1971, the NCI started awarding ''Center of Excellence'' status where excellence in research, cancer prevention and clinical services could be demonstrated. The NCI centres are well staffed with specialists, tend to have high procedure volumes and better access to multidisciplinary consultation and the latest therapies. However, the study's authors say that their relative performance has not been examined to date.

Lead author, Dr. Nancy J O Birkmeyer, concluded: ''Our study suggests that NCI cancer center designation should be weighted less heavily than other factors in deciding where to undergo major cancer surgery''. Patients who do not live near an NCI cancer centre will be able to find a high-volume surgeon with subspecialty training at a high volume cancer centres close to home.

Childhood cancers and prenatal pollution

Most childhood cancers and leukaemias are ''probably initiated'' by prenatal exposure to airborne pollutants, according to a UK professor (*J Epidemiol Community Health* 2005, **59**, 101–05). He suggests a redirection of research efforts relating to childhood cancer.

The study was based on maps of emissions of various chemicals, published by the UK's National Atmospheric Emissions Inventory. Hotspots were identified for 1,3-butadiene, carbon monoxide, PM10, dioxins, benzpyrene, benzene, NMVOC (non-methane volatile organic compounds) and nitrogen oxides.

All children who died before their 16th birthday in the UK between 1966 and 1980 were included in the study. Their home addresses at birth and at death were translated to map references. The analysis focussed on children who had moved more than 1.0 km between birth and death, and who had moved into, or out of, an emissions hotspot. An excess of those who had moved away from a hotspot, versus those who had moved towards one, would suggest an increased risk of cancer prenatally or in early infancy.

''1,3-BUTADIENE AND CARBON MONOXIDE CARRIED THE HIGHEST RISK''

The study found that children born within 1.0 km radium of emissions hotspots were between 2 and 4 times as likely to die of cancer before reaching the age of 16, compared with other children. Proximity to emissions of 1,3-butadiene and carbon monoxide carried the highest risk.

Professor George Knox, Emeritus Professor (University of Birmingham, UK) conducted the study, and said, ''Most childhood cancers are probably initiated by close prenatal encounters with one or more of these high emissions sources. The low atmospheric levels of these substances suggests that the mother may breathe them in, with carcinogens passing across the placenta. But he adds, ''Effective direct exposures in early infancy, through breast milk or even pre-conceptually, cannot be excluded''.

''The main policy implications are a need to regulate carcinogenic atmospheric emissions, especially 1,3-butadiene; and for a redirection of research efforts relating to childhood cancer. This research should now try to determine the exact timings of chemically-determined air-mediated cancer initiations … and to seek engineering and social solutions''.