

or of the amended TEAM trial, which is comparing sequential tamoxifen-exemestane therapy with 5 years of exemestane, to establish which regimen should be preferred. However, the results of these trials are not expected before 2008, but probably they will require a few years more to become mature. By that time, it is unlikely that tamoxifen will still be a current therapeutic option and most patients with endocrine-responsive early breast cancer will have been assigned to an aromatase inhibitor. For now, we can only gamble that, by that time, switching to the “old” tamoxifen or maybe to new selective oestrogen-receptor disruptors might offer a further chance to all those women, in the same way switching to an aromatase inhibitor now offers a little extra hope for the thousands of women who are still receiving tamoxifen.

**Francesco Boccardo, Alessandra Rubagotti*

Department of Medical Oncology, National Cancer Research Institute, Genoa, Italy; and Department of Oncology, Biology and Genetics, University of Genoa Medical School, 16132 Genoa, Italy
f.boccardo@unige.it

AR declares that she has no conflict of interest. FB has received honoraria and travel support from AstraZeneca.

- 1 Coombes RC, Kilbom LS, Snowdon CF, on behalf of the Intergroup Exemestane Study. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; published online Feb 13. DOI:10.1016/S0140-6736(07)60200-1.
- 2 Boccardo F, Rubagotti A, Amoroso D, et al. Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: results of an Italian cooperative study. *J Clin Oncol* 2001; **19**: 4209–15.
- 3 Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole trial. *J Clin Oncol* 2005; **23**: 5138–47.
- 4 Kaufmann M, Jonat W, Hilfrich J, on behalf of the German Adjuvant Breast Cancer Group. Survival benefit of switching to anastrozole after 2 years' treatment with tamoxifen versus continued tamoxifen therapy: the ARNO 95 study. American Society of Clinical Oncology Annual Meeting, Atlanta, Georgia, June 2–6, 2006: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confid=408&bstractID=33783 (accessed Jan 31, 2007).
- 5 Jakesz R, Jonat W, Gnani M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005; **366**: 455–62.
- 6 Jonat W, Gnani M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006; **7**: 991–96.
- 7 Boccardo F, Rubagotti A, Aldrighetti D, et al. Switching to an aromatase inhibitor provides mortality benefit in early breast carcinoma: pooled analysis of two consecutive trials. *Cancer* 2007; published online Feb 12. DOI:10.1002/cncr.22513.
- 8 ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **69**: 60–62.
- 9 Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol* 2007; published online Jan 2. DOI:10.1200/JCO.2006.08.8617.
- 10 Tovey S, Dunne B, Witton CJ, et al. Can molecular markers predict when to implement treatment with aromatase inhibitors in invasive breast cancer? *Clin Cancer Res* 2005; **11**: 4835–42.
- 11 Winer EP, Hudis C, Bounstein HS, et al. American Society of Clinical Oncology Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer: status report 2004. *J Clin Oncol* 2005; **23**: 619–29.
- 12 Punglia RS, Knuntz KM, Winer EP, et al. Optimizing adjuvant endocrine therapy in postmenopausal women with early stage breast cancer: a decision analysis. *J Clin Oncol* 2005; **23**: 5178–87.
- 13 Cuzick J, Sasien P, Howell A. Should aromatase inhibitors be used as initial adjuvant treatment or sequenced after tamoxifen? *Br J Cancer* 2006; **94**: 460–64.
- 14 Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. *Cancer* 2004; **101**: 1311–22.
- 15 Lonning PE. Comparing cost/utility of giving an aromatase inhibitor as monotherapy for 5 years versus sequential administration following 2–3 or 5 years of tamoxifen as adjuvant treatment for postmenopausal breast cancer. *Ann Oncol* 2006; **17**: 217–25.

Traffic-related pollution and lung development in children



The adverse health effects of air pollution are of increasing concern. Many studies show that air pollution causes not only unfavourable respiratory effects in patients with asthma, chronic obstructive pulmonary disease, and other lung conditions, but also cardiovascular effects such as myocardial infarction and stroke. Associations have been recorded for both morbidity and mortality.^{1,2} Of the different air pollutants, particulate matter has emerged as the component most strongly related with health effects, with the size fraction of particles smaller than 2.5 µm being most unfavourable. In urban areas, this fraction is commonly

linked to combustion processes, with traffic as a major contributor.

In today's *Lancet*, William Gauderman and colleagues³ provide evidence that living close to motorways (freeways) in California, USA, leads to reduced lung development in children. In a longitudinal study, more than 3600 children were followed up from age 10 to 18 years with measurements of lung function every year. Children living less than 500 m from motorways had reduced lung-function growth, compared with those living more than 1500 m away. This finding is important because it shows that within communities some children

Published Online
January 26, 2007
DOI:10.1016/S0140-
6736(07)60038-5
See [Articles](#) page 571

The printed journal includes an image merely for illustration

Getty Images

are at higher risk than others. Thus environmental equity is an issue of local rather than regional dimensions.

Could alternative explanations for Gauderman and colleagues' findings be considered? Other studies from the Los Angeles basin have shown that poor children are more likely to attend schools near busy motorways than those from affluent families,⁴ and adjustment for social factors is always difficult in this type of study. Although Gauderman did all he could to take socioeconomic status into account, the effect that social factors might have on lung-function growth is difficult to define, and the possibility for residual confounding remains. Another issue is school location: the study covered the age range of 10–18 years—ie, largely those children attending secondary school, and one line of investigation would have been to measure what preceding exposures at younger school ages might have contributed, because associations with school exposures have been reported in some European studies.^{5,6} The density and composition of the traffic could also have been examined, but the study's power would have been insufficient to address these additional questions in detail. However, these questions should not distract from the major achievement of follow-up of such a large group of children through secondary school with repeated lung-function tests. Furthermore, as Gauderman and co-workers discuss, many studies now implicate close residence to busy roads with adverse respiratory outcomes in children.

Most investigations have used area monitoring of air pollution to relate to health effects. Few studies specifically accounted for the effects of individuals

living close to high emissions from traffic. In their 8-year cohort, Gauderman and colleagues take this context further by showing that poor development of lung function associated with residence within 500 m from a motorway was independent of regional air quality.

The quest to identify what traffic-related components are responsible for specific health effects is important. The roles of fuels, engines, exhaust gases, and particles (as well as components of road and vehicle wear) demand much attention to reduce the biomedical consequences of traffic pollution. Gauderman and co-workers point towards diesel emissions as an important cause in the impaired development of lung function in their cohort. Diesel-engine exhaust contains large quantities of nanoparticles with organic hydrocarbon components on the surface. The primary emissions, on the road and in close vicinity, also include organic vapours and nanoparticles in nucleation mode. Indeed, several human experimental studies^{7,8} with dilute diesel-exhaust show extensive inflammatory effects in the bronchial wall with adverse functional consequences. The underlying mechanisms have been associated with oxidative stress and activation of several mitogen-activated protein kinases and transcription factors, and disturbances in cell functions by the physical and chemical characteristics of diesel exhaust.^{9–11} In one study,¹² diesel-exhaust reactions were reported to extend to disturbances in vascular tone and coagulation.

Gauderman and colleagues' paper does, combined with previous epidemiological studies on adverse health effects of traffic, focus on traffic emissions and risks of living close to major motorways. This finding leads to important questions for society about the structure of the transportation system, engines, fuels, combustion, and road dust in urban areas.

**Thomas Sandström, Bert Brunekreef*

Department of Respiratory Medicine and Allergy, University Hospital, Umeå SE-901 85, Sweden (TS); and Institute for Risk Assessment Sciences, and Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, University of Utrecht, Utrecht, Netherlands (BB)
thomas.sandstrom@lung.umu.se

We declare that we have no conflict of interest.

- 1 Brunekreef B, Holgate ST. Air pollution and health. *Lancet* 2002; **360**: 1233–42.
- 2 Kunzli N, Kaiser R, Medina S, et al. Public-health impact of outdoor and traffic-related air pollution: a European assessment. *Lancet* 2000; **356**: 795–801.

- 3 Gauderman WJ, Vora H, McConnell R, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; published online Jan 26. DOI:10.1016/S0140-6736(07)60037-3.
- 4 Green RS, Smorodinsky S, Kim JJ, McLaughlin R, Ostro B. Proximity of California public schools to busy roads. *Environ Health Perspect* 2004; **112**: 61–66.
- 5 Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knappe M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology* 1997; **8**: 298–303.
- 6 Janssen NA, Brunekreef B, van Vliet P, et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect* 2003; **111**: 1512–18.
- 7 Salvi S, Blomberg A, Rudell B, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999; **159**: 702–09.
- 8 Nordenhall C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur Respir J* 2001; **17**: 909–15.
- 9 Kelly FJ. Dietary antioxidants and environmental stress. *Proc Nutr Soc* 2004; **63**: 579–85.
- 10 Pourazar J, Mudway IS, Samet JM, et al. Diesel exhaust activates redox-sensitive transcription factors and kinases in human airways. *Am J Physiol Lung Cell Mol Physiol* 2005; **289**: L724–30.
- 11 Xia T, Korge P, Weiss JN, et al. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. *Environ Health Perspect* 2004; **112**: 1347–58.
- 12 Mills NL, Tornqvist H, Robinson SD, et al. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation* 2005; **112**: 3930–36.

Maternal fish consumption benefits children's development

The fetal brain grows rapidly in size and complexity during gestation, and at birth weighs about 350 g; in the first two decades of life the brain triples in size. The brain accounts for about 25% of the basal metabolic rate at birth, and is about 50% lipid.^{1,2} This lipid content is predominantly polyunsaturated long-chain fatty acids, some of which are essential fatty acids. These essential fatty acids are precursors of prostaglandins, are incorporated into cell membranes, and have many other roles in the central nervous system. The fetal and neonatal brain receives essential fatty acids either preformed or synthesises them from precursors. Two of the most important essential fatty acids are docosahexaenoic acid and arachidonic acid. Although the developing brain needs large quantities of these nutrients, especially docosahexaenoic acid, the human body cannot synthesise adequate quantities from precursors.³ Consequently, they are mostly obtained from the diet, which makes adequate maternal nutrition very important to the development of the fetal brain. Fish and seafood contain large amounts of essential fatty acids, as does breast milk.⁴ The fatty acid content of the mother's breast milk is determined mostly by her diet.

In today's *Lancet*, Joseph Hibbeln and colleagues⁵ show the value of nutrition in fetal and infant development by associating children's development with their mother's fish consumption. They conclude that higher maternal fish consumption results in children showing better neurological function than children whose mothers ate low amounts or no fish during pregnancy. These results highlight the importance of including fish in the

maternal diet during pregnancy and lend support to the popular opinion that fish is brain food.

Hibbeln and colleagues' study should be of great interest to governmental authorities pondering the relative risks and benefits of fish consumption. All fish contain small amounts of methylmercury in their flesh, but they also contain nutrients essential to brain development, such as essential fatty acids, iodine, choline, and iron. Although methylmercury can be neurotoxic, the amount of exposure that constitutes a toxic dose is not known. The only confirmed cases of prenatal human poisoning by methylmercury from fish consumption happened at Minamata and Niigata, Japan, in the 1950s and 1960s after massive industrial pollution of nearby water.⁶ A subsequent epidemiological study of poisoning in Iraq suggested a risk might be present at exposures of around 10 parts per million measured in maternal hair.⁷ Individuals consuming fish can achieve this concentration. However, in Iraq, exposure was from seed grain treated with methylmercury, and not from fish consumption.

Two subsequent epidemiological studies^{8,9} reported subtle adverse developmental effects at exposures of 4–6 parts per million in maternal hair. None of the individuals in these studies had clinical symptoms or signs of toxic effects. However, when children in the cohorts with the lowest prenatal methylmercury exposures were compared with those with the highest exposures, some neurodevelopmental outcomes showed significant differences in some but not all statistical analyses. The authors attributed these population differences to methylmercury exposure. In one of these populations,

See [Articles](#) page 578