Fetal exposure to dietary carcinogens and risk of childhood cancer

Jos Kleinjans and colleagues summarise the evidence from the NewGeneris project, a European study using biomarkers to assess how maternal diet affects the child

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KEY MESSAGES

- An estimated 175 000 new cancer cases occur globally among children aged 0-14
- The fetus is exposed to dietary carcinogens consumed by the mother during pregnancy
- Exposure of the fetus causes perturbations of the molecular pathways linked with functional markers of carcinogenicity
- Genetic polymorphisms and male sex may predispose to susceptibility to carcinogen exposure before birth and increase risks of developing leukaemia, in particular
- Fetal exposure to dietary carcinogens may also affect birth weight and cause immune suppression

Cancer in childhood is rare. Globally, there are around 175 000 new cancer cases a year among children aged 0-14 years.[1] However, in Europe, since the 1950s the incidence of cancer in this age group has increased by about 1% a year, with leukaemia, brain tumours, and lymphomas accounting for most cases.[2] The increases in incidence of lymphoid leukaemia, in particular, are more apparent in European than in Asian or African children.[3] The development of childhood cancer thus seems to be affected by both genetic and environmental factors. Given that the highest incidences of childhood leukaemia are reported in children younger than 6-7 years, that the latency period of leukaemia in children is relatively short,[4] and that adverse genetic events in utero have been shown to give rise to leukaemia in childhood,[5] we hypothesised that fetal exposure to environmental carcinogens may be an underlying cause. Diet is an important source of carcinogenic compounds because of the accumulation of environmental carcinogens within the food chain (dioxins, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs)), as well as of formation of carcinogens such as PAHs, heterocyclic amines, and acrylamide during baking, frying, and grilling of food.[6] The NewGeneris (Newborns and Genotoxic Exposure Risks) project therefore set out to investigate whether intake of dietary carcinogens by the pregnant mother leads to exposure of the fetus and initiates adverse biological responses that can induce cancer in later childhood.

Investigation of this hypothesis in an epidemiological study would require a huge sample size because of the relatively low incidence of childhood cancer (about 140 cases per million children).[2 3] Case-control studies have been informative but also have limitations.[7] Instead, we designed a biomarker

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based study.[8] We used umbilical cord blood samples from 1151 newborns from mother-child birth cohorts and biobanks in Crete, Denmark, Norway, Spain, and UK to investigate biochemical and cytogenetic markers indicative of prenatal exposure to chemical carcinogens and longer term cancer risk. We focused on fetal exposure to the following dietary carcinogens: acrylamide, PAHs, nitrosamines, fat oxidation metabolites (malondialdehyde), and xenoestrogens (dioxins and dioxin-like PCBs). Here, we summarise the major findings.

Do dietary carcinogens pass the placenta?

For fetal exposure to occur, dietary carcinogens taken in by the mother have to pass through the placenta. We investigated this using perfusion methods on placentas donated by 93 healthy mothers without any reported complications of pregnancy.[9] Although the transfer rates of the different compounds varied, all tested carcinogens readily crossed the placental barrier. Nitrosamines—for example, nitrosodimethylamine—passed through most rapidly, followed by acrylamide and PAHs such as benzo(a)pyrene, with PCB 52 and dioxin being the slowest.[9] However, since placental morphology profoundly changes throughout gestation, data on carcinogen transfer rates from term placenta may not be representative of transfer occurring earlier in gestation.[10] We concluded that the placenta does not protect the fetus against exposure to dietary carcinogens.

Is the fetus actually exposed to dietary carcinogens?

We quantified the presence of selected dietary carcinogens in umbilical cord blood samples taken from 1151 newborns. For nitrosamines, acrylamide, oxidative fat metabolites, and PAHs we assessed exposure by measuring levels of reactive metabolites bound to macromolecules such as DNA and haemoglobin. Plasma levels of dioxins and dioxin-like PCBs were measured with a validated bioassay (DR CALUX). The table shows the levels of these biomarkers of exposure in cord blood. In most infants, fetal exposure was confirmed. We noticed large variations in all biomarkers, with a skewed distribution of exposure across newborns (for instance, acrylamide-haemoglobin adducts ranged from 4.4 to 124.8 pmol/g Hb).[11]

Does fetal exposure induce potentially carcinogenic events?

To assess the cancer risks potentially associated with fetal exposures to selected dietary carcinogens, we measured the numbers of micronuclei in lymphocytes from 467 umbilical cord blood samples. Micronuclei are a cytogenetic biomarker for chromosomal damage and have been prospectively associated with cancer risks in adults occupationally exposed to carcinogenic compounds.[15] We found significant associations between particular features of micronuclei and exposure to oxidative fat metabolites and dioxins and PCBs, predominantly in the highest quarters of exposure.[11]

To investigate further the molecular mechanisms underlying carcinogenic events in utero we determined global gene expression levels in 120 Norwegian neonates in relation to fetal exposure to acrylamide and dioxins. While exposure did not seem to differ between the sexes, we discovered important sex-specific differences in genomic responses, in particular associated with effects on cell cycle and the immune system.[16] Specifically in boys, dioxin exposure was associated with activation of the proinflammatory transcription regulator tumour necrosis factor α, which then induces the nuclear factor-κB; acrylamide exposure was associated with activation of the Wnt pathway, which is associated with uncontrolled cell growth. This may explain the higher incidence of leukaemia[2] and cancer overall among boys.[3]

Subsequently, from these gene expression profiles, we selected 36 genes and developed a high throughput screen based on polymerase chain reaction technology. This allowed us to evaluate the associations of these genes with established fetal exposures in all 1151 newborns for whom we had umbilical cord blood. Compared with the lowest exposure groups, expression of five genes was significantly higher in those with highest exposure to polycyclic aromatic hydrocarbons and six genes for those with highest exposure to fat metabolites. Expression levels were significantly lower for seven genes in those with highest exposure to dioxins compared with the lowest category.[11] The affected genes have roles in cell cycle regulation and apoptosis, which are generic processes involved in carcinogenesis.

Overall, fetal exposure to selected dietary carcinogens seems to induce molecular events that indicate increased cancer risks, thus supporting the hypothesis that childhood cancer, in particular leukaemia among boys, is causally related to the dietary intake of carcinogenic substances by their mothers during pregnancy.

Are particular children more susceptible to cancer risks?

Childhood cancer remains uncommon despite widespread exposure to dietary carcinogens in utero. This suggests that particular children may be more susceptible to the cancerous effects of toxic chemicals.[17] Such increased susceptibility may be genetically predisposed—

Median (range) exposure to dietary (pre)carcinogens in newborns and maternal dietary intake during pregnancy

Carcinogen (biomarker)	Cord blood biomarker level	Maternal daily dietary intake*	Foods with high levels
Acrylamide (acrylamide-haemoglobin adducts)	14.4 (4.4-124.8) pmol/g Hb	22 (1-135) µg	Deep fried potato products (crisps, french fries)
			Crisp breads, biscuits, crackers
			Coffee
Polycyclic aromatic hydrocarbons (bulky DNA adducts)	8.4 (0.6-116.6) 10-8 nucleotides	180 (42-717) ng	Grilled/barbecued meats
			Smoked and processed fish
			Smoked and processed meat
Oxidative fat metabolites (M1dG-DNA adducts)	34.2 (0.5-324.7) 10-9 nucleotides	Omega 6 fatty acids 11.3 (1.2-77.0) g	Vegetable oils (soya, rape, sunflower)
			Fatty meat
			Eggs
Nitrosamines (O^6-MG-DNA adducts)	0.40 (0.08-3.03) 10-8 nucleotides	N-nitrosodimethylamine 82 (2-547) ng	Processed meat
			Preserved fish
			Smoked meat
			Smoked fish
Dioxin/PCBs (plasma DR CALUX)	0.13 (0.01-104) pg/ml†	77.2 (5.1-945.5) pg†	Fatty meat
			Fatty fish
			Full fat milk and dairy products

*Derived from the NewGeneris database on dietary consumption patterns taken from food frequency questionnaires and data on chemical levels in food.[12-14]
†2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxic equivalency quotients.

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- Research: Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring (*BMJ* 2013;347:f4539)
- Research: Maternal dietary patterns and preterm delivery (*BMJ* 2014;348:g1446)

some people may lack the gene activity for, say, detoxifying carcinogens or repairing induced DNA damage, or express a higher activity in metabolic transformation of carcinogens into DNA damaging daughter compounds. Relevant genes may be polymorphic in the general population, being non-homogeneously distributed at frequencies of 5-40%. Carriers of such single nucleotide polymorphisms (SNPs) may be prone to increased cancer risks after exposure to carcinogenic agents.[18]

To investigate whether genetic predisposition increased susceptibility to fetal exposure to carcinogens, we analysed cord blood DNA from 435 subjects using a genome-wide association method.[19] We found a strong signal that the folate hydrolase 1 (*FOLH1)* gene interacted with the association between fetal exposure to dioxin related androgens and frequencies of micronuclei. The *FOLH1* polymorphism may cause low serum levels of folate thus leading to chromosome instability and formation of micronuclei. In addition, polymorphisms in the epoxyhydrolase 1/2 (*EPHX1/2)* and cytochrome p450 2E1 (*CYP2E1*) genes coding for metabolic enzymes, which may bioactivate precarcinogenic chemicals, seem to be associated with the micronuclei frequencies.[11]

In conclusion, although the evidence is still limited, our data suggest some genetic predisposition to risk of childhood cancer associated with fetal exposure to dietary carcinogens.

Are there other effects on health?

We also investigated the effect of fetal exposure to dietary carcinogens on birth weight, head circumference, and gestational age. Fetal exposure to acrylamide seemed associated with a reduction in birth weight and head circumference (n=1101).[20] Biomarkers of exposure to PAHs (n=612) were associated with lower birth weight only in newborns from Denmark, England, and Norway.[21] In addition, birth weight was lower in infants in the medium and high thirds of dioxin and dioxin-like PCB levels in cord blood (n=967) compared with those in the lowest third.[12] Furthermore, gestational age was shorter by about half a week in the highest compared with the lowest exposure levels; this association seemed to be stronger for boys than for girls. Reduced birth weight is regarded as a risk factor for cardiovascular disease, type 2 diabetes, and osteoporosis in later life,[22] while reduced head circumference at birth may be related to delayed neurodevelopment.[23]

We propose that national food safety agencies consider exposure risks in more detail and implement policy measures where appropriate

Furthermore, we showed that maternal intake of dioxin and PCBs estimated from food frequency questionnaires is associated with immunotoxic events during early childhood. In 111 newborns from the Norwegian cohort, dioxin exposure was associated with gene expression responses in cord blood cells and with reduced measles vaccination responses at age 3 years.[24] Overall, the functions of affected genes—for instance, those belonging to the HLA system related to antibody production[25]—pointed towards immunosuppression, girls showing more immune related genes deregulated in association with dioxin and PCB exposure than boys.

Based on the above results, fetal exposure to dietary carcinogens may have other adverse effects on health in addition to cancer risk.

Can pregnant women reduce their risk of exposure?

The NewGeneris project suggests that pregnant women's consumption of carcinogens present in the European diet results in measurable fetal exposures. Furthermore, such exposure seems to result in molecular and functional changes that are thought to be biomarkers for the risk of developing cancer and other diseases during childhood and later life. We observed higher susceptibilities among boys, as well as among carriers of particular gene polymorphisms, suggesting that genetic predisposition may contribute to health risks. Such risks can be reduced by decreasing the intake of dietary carcinogens. Although pregnant women can limit consumption by avoiding foods such as processed meats and fried and grilled food, eliminating carcinogens altogether is difficult because of their ubiquity in the diet.

Food manufacturers could have a role in reducing the presence of carcinogenic agents. For instance, manufacturers of French fries and crisps could switch to low sugar potato varieties to reduce the presence of acrylamide, which is formed during deep frying by the reaction of asparagine and reducing sugars (both naturally occurring in potatoes). Reduction of use of nitrite for curing meat products would also lead to less formation of nitrosamines in the stomach. For carcinogens that are present in multiple types of food, such as dioxin-like PCBs which are generically present in meat and fish as well as in milk and milk products,[13] food manufacturers could be required to assess the levels of these compounds in raw products and take preventive measures. We propose that national food safety agencies consider exposure risks in more detail and implement policy measures where appropriate.

In general, our findings support the recommendation to pregnant mothers to eat a well balanced diet. Such a diet also has benefits for the child by reducing the risks of preterm delivery,[26] low birth weight,[27] childhood leukaemia,[7] and adult cardiovascular disease.[28] It should also not be forgotten that smoking and alcohol intake during pregnancy pose the largest health risks to the unborn child.

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