Bulky DNA adducts, 4-aminobiphenyl-haemoglobin adducts and diet in the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study

Marco Peluso\(^1\), Luisa Airoldi\(^2\), Armelle Munnia\(^1\), Alessandro Colombi\(^2\), Fabrizio Veglia\(^3\), Herman Autrup\(^4\), Alison Dunning\(^5\), Seymour Garte\(^6\), Emmanuelle Gormally\(^7\), Christian Malaveille\(^7\), Giuseppe Matullo\(^3\), Kim Overvad\(^8\), Ole Raaschou-Nielsen\(^9\), Jacob Linseisen\(^11\), Heiner Boeing\(^12\), Antonia Trichopoulou\(^13\), Domenico Palli\(^14\), Vittorio Krogh\(^15\), Rosario Tumino\(^16\), Salvatore Panico\(^17\), Bas H. Bueno-De-Mesquita\(^18\), Petra H. Peeters\(^19\), Merethe Kumle\(^20\), Antonio Agudo\(^21\), Carmen Martínez\(^22\), Miren Dorronsoro\(^23\), Aurelio Barcicarte\(^24\), Maria Jose Tormo\(^25\), José Ramón Quiros\(^26\), Goran Berglund\(^27\), Bengt Jarvholm\(^28\), Nicholas E. Day\(^29\), Timothy J. Key\(^30\), Rodolfo Saracci\(^31\), Rudolf Kaaks\(^32\), Elio Riboli\(^33\), Shelia Bingham\(^29\) and Paolo Vineis\(^34,35\)*

\(^1\)Cancer Risk Factor Branch, Analytical and Biomolecular Cytology Unit, CSPO-Scientific Institute of Tuscany, Florence, Italy
\(^2\)Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy
\(^3\)ISI Foundation, Turin, Italy
\(^4\)Department of Environmental and Occupational Medicine, Aarhus, Denmark
\(^5\)Department of Oncology, University of Cambridge, Cambridge, UK
\(^6\)Genetics Research Institute, Milan, Italy
\(^7\)International Agency for Research on Cancer, Lyon, France
\(^8\)Department of Clinical Epidemiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark
\(^9\)Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark
\(^10\)INSERM (Institut National de la Santé et de la Recherche Médicale), ERI 20, EA 4045, and Institut Gustave Roussy, Villejuif, F-94805, France
\(^11\)Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany
\(^12\)German Institute of Human Nutrition, Potsdam-Rehbrücke, Germany
\(^13\)Department of Hygiene and Epidemiology, Medical School, University of Athens, Athens, Greece
\(^14\)Molecular and Nutritional Epidemiology Unit, CSPO-Scientific Institute of Cancer Prevention Tuscany Region, Florence, Italy
\(^15\)Division of Environmental Epidemiology, National Cancer Institute, Milan, Italy
\(^16\)Cancer Registry, Azienda Ospedaliera ‘Civile MP Arezzo’, Ragusa, Italy
\(^17\)Dipartimento di Medicina Clinica e Sperimentale, Università Federico II, Naples, Italy
\(^18\)Centre for Nutrition and Health, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
\(^19\)Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands
\(^20\)Institute of Community Medicine, University of Tromso, Tromso, Norway
\(^21\)Department of Epidemiology, Catalan Institute of Oncology, Barcelona, Spain
\(^22\)Andalusian School of Public Health, Granada, Spain
\(^23\)Department of Public Health of Guipuzkoa, San Sebastian, Spain
\(^24\)Public Health Institute, Navarra, Spain
\(^25\)Epidemiology Department, Murcia Health Council, Murcia, Spain
\(^26\)Dirección General de Salud Pública, Consejería de Salud y Servicios Sanitarios Asturias, Oviedo, Spain
\(^27\)Malmó Diet and Cancer Study, Lund University, Malmö, Sweden
\(^28\)Department of Nutritional Research, University of Umeå, Umeå, Sweden
\(^29\)MRC Dunn Human Nutrition Unit, Cambridge University, UK
\(^30\)Cancer Research UK Epidemiology Unit, University of Oxford, Oxford, UK
\(^31\)IFC National Research Council, Pisa, Italy
\(^32\)Division of Epidemiology, DKFZ Heidelberg, Germany

Abbreviations: 4-ABP, 4-aminobiphenyl; EPIC, European Prospective Investigation into Cancer and Nutrition; PAH, polycyclic aromatic hydrocarbons.

*Corresponding author: Dr P. Vineis, fax +44 20 7594 3196, email p.vineis@imperial.ac.uk
In contrast to some extensively examined food mutagens, for example, aflatoxins, N-nitrosamines and heterocyclic amines, some other food contaminants, in particular polycyclic aromatic hydrocarbons (PAH) and other aromatic compounds, have received less attention. Therefore, exploring the relationships between dietary habits and the levels of biomarkers related to exposure to aromatic compounds is highly relevant. We have investigated in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort the association between dietary items (food groups and nutrients) and aromatic DNA adducts and 4-aminobiphenyl-Hb adducts. Both types of adducts are biomarkers of carcinogen exposure and possibly of cancer risk, and were measured, respectively, in leucocytes and erythrocytes of 1086 (DNA adducts) and 190 (Hb adducts) non-smokers. An inverse, statistically significant, association has been found between DNA adduct levels and dietary fibre intake (P = 0.04) and vitamin E (P = 0.04) and alcohol (P = 0.03) but not with other nutrients or food groups. Also, an inverse association between fibre and fruit intake, and BMI and 4-aminobiphenyl-Hb adducts (P = 0.04, 0.04, and 0.03 respectively) was observed. After multivariate regression analysis these inverse correlations remained statistically significant, except for the correlation adducts vs. fruit intake. The present study suggests that fibre intake in the usual range can modify the level of DNA or Hb aromatic adducts, but such role seems to be quantitatively modest. Fibres could reduce the formation of DNA adducts in different manners, by diluting potential food mutagens and carcinogens in the gastrointestinal tract, by speeding their transit through the colon and by binding carcinogenic substances.

DNA adducts: Haemoglobin adducts: Non-smokers: Fibre intake: Air pollution

Most cancers result from a complex interaction of environmental factors, genetic susceptibility and lifestyle factors. Diet is an important component of lifestyle, and its role in the maintenance of good health and as a determinant of different types of chronic diseases, including cancer, has been extensively studied. Diets that emphasise the consumption of whole-grain foods, legumes, vegetables and fresh fruits and that limit animal fat have been associated with decreased cancer risk. Dietary patterns with high intake of fibres have also emerged as possible important preventive factors for cancer. On the other hand, diet can contribute to cancer risk through the consumption of food mutagens, contained in contaminated foods or generated by frying, toasting and broiling of certain foods. In contrast to some extensively examined food mutagens, for example, aflatoxins, N-nitrosamines and heterocyclic amines, some other food contaminants, in particular polycyclic aromatic hydrocarbons (PAH) and other aromatic compounds, have received less attention. PAH may occur in fried and charcoal-grilled meat or in the food chain as a result of environmental pollution. PAH are an important class of carcinogens, capable of inducing the formation of DNA adducts leading to DNA damage after metabolic activation. Targets for PAH carcinogenicity are several organs, including lung and bladder. Some evidence has been also reported for an association between dietary PAH and colon cancer or adenomas. In addition, increased levels of bulky DNA adducts have been detected in the colon mucosa of colon cancer patients and in early stages of colon carcinogenesis. 4-Aminobiphenyl (4-ABP) is a human bladder carcinogen formed during tobacco combustion, and detected both in main- and side-stream smoke. Although tobacco smoke is the main source of 4-ABP human exposure, additional sources are known that may contribute to the total burden of human exposure, including diesel exhaust and heated cooking oils. Upon metabolic activation, 4-ABP reactive species bind covalently to DNA to form adducts, that, if not repaired, may start the process of carcinogenesis. 4-ABP reactive species in the body also bind to other macromolecules, including Hb.

Exploring the relationships between dietary habits and the levels of biomarkers related to exposure to aromatic compounds is highly relevant. Food can be the source of mutagenic aromatic compounds, but it can also exert a protective effect over the genotoxic potential of certain compounds. In particular, an inverse association between fruit and/or vegetable intake and carcinogen-DNA adducts has been recently reported, including observations in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (limited to the Italian branch).

In the present study, we have investigated in the EPIC cohort the association between dietary items and bulky DNA adducts and 4-ABP-Hb adducts measured, respectively, in leucocytes and erythrocytes of non-smokers.

Subjects and methods

Selection of subjects and collection of specimens

EPIC is a multicentre European study, coordinated by the International Agency for Research on Cancer, Lyon, in which more than 500 000 healthy volunteers were recruited in ten European countries (France, Denmark, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, UK) corresponding to twenty-three recruitment centres. The cohort includes subjects of both sexes, mostly in the age range 35–74 years at recruitment. Recruitment took place between 1993 and 1998. Detailed dietary and lifestyle...
DNA and haemoglobin adducts and fibre intake

Dietary variables

Dietary information on the frequency of consumption of more than 120 foods and drinks has been obtained by dietary questionnaires developed and validated in a pilot phase in each participating country. At enrolment, weight, height, and waist and hip circumferences have been measured for each participant. Detailed information has been collected on reproductive history, physical activity, smoking and alcohol drinking, with selective ion monitoring as its pentafluoroacyl derivative, by high-resolution GC-negative ion chemical ionisation-MS after alkaline hydrolysis of the adducted Hb, and quantified by parent arylamine

Results

Table 1 shows the mean levels and standard deviations of bulky DNA adducts and 4-ABP-Hb adducts, by relevant demographic variables. As it has already been stressed\(^{23}\), one limitation of the adduct technology is the large inter-individual variability (large standard deviations). Table 2 shows the mean levels of DNA and Hb adducts below and above the median levels of relevant dietary or anthropometric variables. For Hb adducts there were no appreciable differences for any dietary variable except for fibres, fruit and BMI.
Table 1. DNA and 4-aminobiphenyl (4-ABP)-Hb adducts, by demographic variables and smoking
(Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Subject (n)</th>
<th>DNA adducts (× 10&lt;sup&gt;5&lt;/sup&gt;)</th>
<th>4-ABP adducts (pg/g Hb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>1086</td>
<td>190</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.71</td>
<td>0.55</td>
</tr>
<tr>
<td>Men</td>
<td>0.68</td>
<td>0.54</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55</td>
<td>0.69</td>
<td>0.61</td>
</tr>
<tr>
<td>55–64</td>
<td>0.68</td>
<td>0.53</td>
</tr>
<tr>
<td>65+</td>
<td>0.71</td>
<td>0.52</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.71</td>
<td>0.57</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.69</td>
<td>0.52</td>
</tr>
</tbody>
</table>

The distribution was skewed for both types of adducts, but particularly for Hb adducts, and the analyses were repeated after log-transformation, with only slight changes. Both types of adducts, but particularly Hb adducts, show lower mean levels for higher fibre intakes. Table 3 shows correlation coefficients between adduct levels and selected dietary variables. Statistically significant associations are evident for DNA adducts and the intake of fibres (correlation coefficient −0.067; P=0.02) and for Hb adducts and the intake of fibres (correlation coefficient −0.15; P=0.03) and fruit (correlation coefficient −0.15; P=0.04). No association was found between either adduct type and folate intake.

Table 2. Mean levels of bulky DNA adducts or 4-aminobiphenyl (4-ABP)-Hb adducts below and above the median level of fibre intake and other selected dietary variables and BMI (one or two missing values depending on item)
(Mean values with their standard errors)

<table>
<thead>
<tr>
<th>Adducts</th>
<th>Below median</th>
<th>Above median</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibres</td>
<td>545</td>
<td>539</td>
<td>0.067; P=0.025</td>
</tr>
<tr>
<td>Fruit</td>
<td>528</td>
<td>557</td>
<td>0.023; P=0.15</td>
</tr>
<tr>
<td>Vegetables</td>
<td>548</td>
<td>537</td>
<td>0.024; P=0.43</td>
</tr>
<tr>
<td>Legumes</td>
<td>521</td>
<td>564</td>
<td>0.021; P=0.04</td>
</tr>
<tr>
<td>Alcohol</td>
<td>500</td>
<td>584</td>
<td>0.024; P=0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>552</td>
<td>533</td>
<td>0.024; P=0.78</td>
</tr>
<tr>
<td>Energy intake</td>
<td>522</td>
<td>563</td>
<td>0.025; P=0.12</td>
</tr>
<tr>
<td>4-ABP-Hb adducts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibres</td>
<td>89</td>
<td>93</td>
<td>6.77; P=0.07</td>
</tr>
<tr>
<td>Fruit</td>
<td>92</td>
<td>96</td>
<td>5.76; P=0.11</td>
</tr>
<tr>
<td>BMI</td>
<td>96</td>
<td>92</td>
<td>6.56; P=0.14</td>
</tr>
</tbody>
</table>

* Based on t test.

Table 3. Correlation coefficients between selected dietary variables and adduct levels (Pearson correlation coefficients and P values)

<table>
<thead>
<tr>
<th>Adducts</th>
<th>Vegetables</th>
<th>Legumes</th>
<th>Fruit</th>
<th>Fibres</th>
<th>Vitamin C</th>
<th>Vitamin E</th>
<th>β-Carotene</th>
<th>Folate</th>
<th>Alcohol</th>
<th>BMI</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson correlation coefficients</td>
<td>−0.029</td>
<td>0.010</td>
<td>−0.008</td>
<td>−0.067</td>
<td>−0.009</td>
<td>−0.061</td>
<td>−0.040</td>
<td>−0.06</td>
<td>−0.07</td>
<td>−0.04</td>
<td>−0.000</td>
</tr>
<tr>
<td>P</td>
<td>0.32</td>
<td>0.73</td>
<td>0.78</td>
<td>0.02</td>
<td>0.74</td>
<td>0.04</td>
<td>0.14</td>
<td>0.01</td>
<td>0.03</td>
<td>0.22</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Discussion
In the EPIC investigation we have recently examined prospectively the ability of bulky DNA adducts to predict cancer and we have found that leucocyte DNA adducts may predict lung cancer risk among never and former smokers(23). In addition we have provided evidence that, particularly among women, elevated 4-ABP-Hb adducts may help identify subjects at higher risk of environmental tobacco smoke-related cancers(24).

In the present study, we have investigated the association between dietary items and bulky DNA adducts and 4-ABP-Hb adducts measured, respectively, in leucocytes and...
DNA adducts and haemoglobin adducts and fibre intake

Table 4. Multivariate regression models*

<table>
<thead>
<tr>
<th>DNA adducts</th>
<th>Parameter estimate</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>0.000</td>
<td>0.17</td>
<td>0.857</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.01</td>
<td>-0.43</td>
<td>0.67</td>
</tr>
<tr>
<td>Country</td>
<td>-2.92</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Smoking status†</td>
<td>0.03</td>
<td>-0.74</td>
<td>0.46</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>-0.002</td>
<td>1.83</td>
<td>0.07</td>
</tr>
<tr>
<td>Energy (MET)</td>
<td>0.000</td>
<td>0.49</td>
<td>0.62</td>
</tr>
<tr>
<td>Fibres (g/d)</td>
<td>-0.006</td>
<td>-2.28</td>
<td>0.022</td>
</tr>
<tr>
<td>After inclusion of ozone</td>
<td>Fibres</td>
<td>-0.0054</td>
<td>-1.97</td>
</tr>
<tr>
<td>Ozone (µg/m³)</td>
<td>0.007</td>
<td>1.95</td>
<td>0.051</td>
</tr>
<tr>
<td>After stratification by smoking habits</td>
<td>Fibres (non-smokers)</td>
<td>-0.002</td>
<td>-0.55</td>
</tr>
<tr>
<td>Fibres (former smokers)</td>
<td>-0.009</td>
<td>2.39</td>
<td>0.023</td>
</tr>
<tr>
<td>4-BP-Hb adducts</td>
<td>Age (continuous)</td>
<td>-0.48</td>
<td>-1.06</td>
</tr>
<tr>
<td>Sex</td>
<td>11.3</td>
<td>1.41</td>
<td>0.16</td>
</tr>
<tr>
<td>Country</td>
<td>-1.19</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Smoking status†</td>
<td>1.07</td>
<td>0.13</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI</td>
<td>-2.18</td>
<td>-2.59</td>
<td>0.011</td>
</tr>
<tr>
<td>Fibres</td>
<td>0.94</td>
<td>-2.21</td>
<td>0.035</td>
</tr>
</tbody>
</table>

MET, metabolic equivalent values; ABP, aminobiphenyl.

* The dependent variable is DNA adducts or 4-ABP-Hb adducts. All independent variables except sex, country and smoking (never or ex-smoker) are continuous. Ozone was measured in 1990–98.
† Former v. never smokers.
‡ After log-transformation of DNA adducts, t = -2.02 (P = 0.04).
§ After log-transformation of DNA adducts, t = -2.14 (P = 0.03).
¶ After log-transformation of fibres (g/d), t = -1.46 (P = 0.15).
‖ After log-transformation of 4-BP-Hb adducts, t = -1.95 (P = 0.05).

...erythrocytes of non-smokers. The rationale came from the presence of mutagenic PAH and aromatic compounds in food, and from previous observations relating high intakes of fruit and vegetables to decreased levels of adducts. No dietary item was associated with the levels of aromatic DNA or Hb adducts, except the intake of fibres, independently of levels of vitamins or folate intake.

When exposure to an air pollutant, ozone, was included into the regression model, the role of fibres was slightly weakened. Also, the association with fibres was present only in former smokers, an observation that suggests complex interactions between exposure to carcinogens and to protective compounds. In a study in healthy volunteers we have found that diet can have an important effect on the induction of DNA repair genes (31); possible mechanisms for the inverse association between case or control status, and the level of adducts (below or above the median value) was stronger in subjects who consumed less than one portion of vegetables per day (OR 4.98 for consumers of two portions per day; OR 1.97 for consumers of three or more portions per day). In another study among healthy subjects, inverse associations emerged between levels of bulky DNA adducts and plasma retinol (P = 0.02), α-tocopherol (P = 0.04) and γ-tocopherol (P = 0.03), but not carotenoids (except a borderline inverse association with β-carotene; P = 0.08) (27).

Concerning 4-ABP adducts, in a previous study among bladder cancer patients we found that 4-ABP-DNA adducts in bladder biopsies were inversely related to fruit and vegetable intake (20). In a more recent study we reported an inverse correlation also between 4-ABP-Hb adduct levels and fruit and vegetable consumption in non-smokers (21). Moreover, 4-ABP-Hb adducts were reportedly modulated by the intake of carotenoids in the control population of a large case-control study on smoking-related bladder cancer, this effect being confined to current smokers (22).

Possible mechanisms for the inverse association between fibre intake and adduct formation include:

1. Bacterial fermentation of dietary fibre produces SCFA, including butyrate, that can protect the colonic mucosa barrier (23), increase apoptotic response to genotoxic carcinogens (30) and enhance glutathione transferase π expression (31).
2. Dietary fibre may decrease the levels of DNA damage by enhancing the action of antioxidant components contained in phytochemicals; the protective effects may be mainly due to some components, such as phenolic polysaccharides and polyphenols, which are present in the cell walls of various plants and that can be released by bacterial enzymes in the colon. Indeed, flavonoids, polyphenols and other plant compounds have been shown to be capable of inhibiting DNA adduct formation (24,33) possibly by their antioxidant activity or by interfering with the metabolic pathways of activation/detoxification of food mutagens (33).
3. The protective effects of an increased intake of fibre may be related to increased faecal bulk or reduced transit time (34), thereby diluting potential toxins and carcinogens and reducing their contact time with the colonic epithelium.

It is unlikely that the present results can be explained by bias or confounding. The study had a prospective nature, and dietary ascertainment took place several years before adduct measurement, which was blind as to dietary variables. Alcohol and several of the potential confounding factors, such as age, sex, smoking status, BMI, energy intake, intake of fruit, legumes, vegetables, meat, vitamins and folate have also been evaluated in the present study.

In summary, after finding a clear protective effect of fibres in colon carcinogenesis (35), the present study from the same population (the EPIC prospective study) suggests that fibres can modify the levels of bulky DNA adducts and 4-ABP-Hb adducts.

Acknowledgements

We are grateful to Julie Britton for comments on the manuscript.

...DNA repair genes (31); possible mechanisms for the inverse association between case or control status, and the level of adducts (below or above the median value) was stronger in subjects who consumed less than one portion of vegetables per day (OR 4.98 for consumers of two portions per day; OR 1.97 for consumers of three or more portions per day). In another study among healthy subjects, inverse associations emerged between levels of bulky DNA adducts and plasma retinol (P = 0.02), α-tocopherol (P = 0.04) and γ-tocopherol (P = 0.03), but not carotenoids (except a borderline inverse association with β-carotene; P = 0.08) (27).

Concerning 4-ABP adducts, in a previous study among bladder cancer patients we found that 4-ABP-DNA adducts in bladder biopsies were inversely related to fruit and vegetable intake (20). In a more recent study we reported an inverse correlation also between 4-ABP-Hb adduct levels and fruit and vegetable consumption in non-smokers (21). Moreover, 4-ABP-Hb adducts were reportedly modulated by the intake of carotenoids in the control population of a large case-control study on smoking-related bladder cancer, this effect being confined to current smokers (22).

Possible mechanisms for the inverse association between fibre intake and adduct formation include:

1. Bacterial fermentation of dietary fibre produces SCFA, including butyrate, that can protect the colonic mucosa barrier (23), increase apoptotic response to genotoxic carcinogens (30) and enhance glutathione transferase π expression (31).
2. Dietary fibre may decrease the levels of DNA damage by enhancing the action of antioxidant components contained in phytochemicals; the protective effects may be mainly due to some components, such as phenolic polysaccharides and polyphenols, which are present in the cell walls of various plants and that can be released by bacterial enzymes in the colon. Indeed, flavonoids, polyphenols and other plant compounds have been shown to be capable of inhibiting DNA adduct formation (24,33) possibly by their antioxidant activity or by interfering with the metabolic pathways of activation/detoxification of food mutagens (33).
3. The protective effects of an increased intake of fibre may be related to increased faecal bulk or reduced transit time (34), thereby diluting potential toxins and carcinogens and reducing their contact time with the colonic epithelium.

It is unlikely that the present results can be explained by bias or confounding. The study had a prospective nature, and dietary ascertainment took place several years before adduct measurement, which was blind as to dietary variables. Alcohol and several of the potential confounding factors, such as age, sex, smoking status, BMI, energy intake, intake of fruit, legumes, vegetables, meat, vitamins and folate have also been evaluated in the present study.

In summary, after finding a clear protective effect of fibres in colon carcinogenesis (35), the present study from the same population (the EPIC prospective study) suggests that fibres can modify the levels of bulky DNA adducts and 4-ABP-Hb adducts.

Acknowledgements

We are grateful to Julie Britton for comments on the manuscript.
This paper was made possible by a grant of the European Community (5th Framework Programme) to P. V. (grant QLK4–CT–1999–00927) and a grant of the Compagnia di San Paolo to the ISI Foundation. All authors are independent from funders. Mortality data for the Netherlands were obtained from Statistics Netherlands.

Also, the work described in the paper was carried out with the financial support of: Europe Against Cancer Program of the European Commission (SANCO); ISCHI, Red de Centros RCESP, C03/09; Deutsche Krebshilfe; Deutsches Krebsforschungszentrum; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health; Spanish Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra; Cancer Research UK; Medical Research Council, UK; Stroke Association, UK; British Heart Foundation; Department of Health, UK; Food Standards Agency, UK; Wellcome Trust, UK; Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer (AIRC); Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports; World Cancer Research Fund; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skåne, Sweden; Norwegian Cancer Society; Research Council of Norway.

There are no conflicts of interests to declare.

Individual authors’ contributions were: M. P. and A. M. performed the analysis of DNA adducts; L. A. and A. C. analysed Hb adducts; F. V. performed the statistical analyses; K. O., O. R.-N., F. C.-C., J. L., H. B., A. T., D. P., V. K., R. T., S. P., B. H. B.-D.-M., P. H. P., M. K., A. A., C. Martinez, M. D., A. B., M. J. T., J. R. Q., G. B., L. J., B. J., N. E. D., T. J. K., R. S., R. K. and S. B. collected the data in the local EPIC centres; H. A., A. D., S. G., E. G., C. Malaveille and G. M. were part of the working group that performed laboratory analyses in GenAir and contributed to the interpretation of the results; E. R. is the EPIC coordinator; P. V. coordinated the GenAir investigation and wrote the manuscript with M. P. and L. A.

References


