The Role of Nutrition in Preventing and Treating Breast and Prostate Cancer

The European Prospective Investigation into Cancer and Nutrition (EPIC): Plans and Progress¹,²

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The hypothesis that diet and related metabolic, anthropometric and hormonal factors could play a role in cancer etiology was originally supported by a series of early case-control studies, geographical correlation studies (also called ecological studies) (NRC 1982) as well as pioneering work on rodents in experimental laboratory studies carried out in the 1940s (Tannenbaum 1940a, 1940b, 1942a and 1942b). During the first half of the century, several researchers noticed that overfed rodents were less resistant to the growth of transplanted tumors (Rous 1914) and more sensitive to the effect of chemical carcinogens (Tannenbaum 1942a).

Several decades later, correlation studies showed that incidence (and mortality from) cancer of the breast, colorectum and prostate were positively correlated with the foods most typically consumed in Western societies (i.e., meat, total and animal fat, simple sugars) and negatively correlated with the consumption of various vegetable foods (grains, cereals and vegetable fiber) (Armstrong and Doll 1975). Geographical correlation studies can indicate only that disease risk and the prevalence of a given factor are correlated across different populations; they are limited by the methodological and practical possibility of taking into account confounding factors that may create spurious correlations at the population level. During the past 20 years, a considerable number of retrospective case-control and, more recently, prospective cohort studies have been conducted to investigate whether, in each given population, these dietary factors were effectively related to cancer risk at the individual level.

Results of epidemiologic and experimental studies on nutrition and cancer have been reviewed in depth in recent years by three independent expert committees as follows:

- One in the UK, the Committee on Medical Aspects of Food and Nutrition Policy (COMA Working Group on Diet and Cancer 1998);
- One in France, the commission Prévention des Cancers par l’Alimentation of the Centre National d’Etudes et de Recommandations sur la Nutrition et l’Alimentation (CNERNA-CNRS-INRA) (Riboli et al. 1996);
- One at the international level, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 1997).

The three independent review committees reached broadly similar conclusions. Regarding dietary composition, the three reports agree that the most clearly identified associations are those between the consumption of vegetables and fruit and reduced risk of various cancers. These protective effects have been seen most consistently in studies on cancers of the digestive and respiratory tracts. Frequent, daily consumption of both vegetables and fruit is associated most strongly with a reduction in risk of cancers of the mouth, pharynx, larynx, esophagus, stomach and lung, whereas only consumption of vegetables, but not of fruit, is linked to a reduction in risk of colorectal cancer.

Regarding foods that have been identified consistently as being associated with increased cancer risk, the list is much shorter and is limited to meat and Cantonese-style salted fish. Red meat, mainly beef, but not poultry and fish, is associated with a modest increase in colorectal cancer risk. Consumption of Cantonese-style salted fish has been found to be associated with the risk of nasopharyngeal cancer, which is very frequent in some populations of south-east Asia, particularly southern China, but extremely rare in most other parts of the world.

Regarding fruit, vegetables and red meat, the three reports agreed on an important point, i.e., although their association with cancer risk can be considered to be reasonably well established on the basis of epidemiologic studies, no definite clear explanation exists for the biological mechanisms involved, even though a large number of experimental studies have been carried out and many different mechanisms have been tested on in vitro and in vivo models.

This conclusion leads to two main recommendations. First, it implies that no scientific support exists for a proven cancer-preventive effect of dietary supplements containing various cocktails of vitamins and minerals also found in vegetables and fruits. The only sound recommendation is therefore to eat lots of fruit and vegetables regularly. Second, it implies that more research is required on the biological links between vegetables and fruits and the carcinogenesis process, particularly with randomized supplementation trials and observational epidemiologic studies.

Another growing and promising area of research concerns...
the relationship among anthropometric characteristics, physical activity and cancer risk. The first evidence that overweight may be linked to increased cancer risk dates back to the 1930s when Tannenbaum (1940a) conducted a study on mortality in relation to height and weight using the data of various life insurance companies in the United States. Epidemiologic studies conducted during the past 20 years have shown with various degrees of consistency that excess body mass (usually estimated as weight/height\(^2\), or body mass index) is associated with increased risk of cancer of the endometrium, breast, colon and, possibly, kidney.

Recently, several prospective studies in which blood samples were collected and stored at baseline from healthy subjects have shown that high prediagnostic levels of endogenous steroid hormones, mainly estrogens and testosterone, are associated with a three- to sixfold increase in breast cancer risk (Berrino et al. 1996, Dorgan et al. 1996, Hankinson et al. 1998, Toniolo et al. 1995), whereas one study showed that high testosterone levels increase prostate cancer risk (Gann et al. 1996). These studies also found that low levels of sex hormone binding globulin (SHBG)\(^3\) are also associated with higher risk of breast cancer; SHBG is synthesized in the liver and its production is down-regulated by insulin. The link among overweight, a sedentary lifestyle and cancer risk may well be mediated in part by these insulin-SHBG-steroid hormone pathways for cancer of the breast (Kaaks 1996), colon (Giovannucci 1995), prostate and possibly other cancers.

An additional important link between diet and cancer risk may exist through the control of the production of insulin-like growth factors (IGF) and their binding proteins (IGF-BP). Recent studies found that high levels of IGF\(_1\), (adjusted over the levels of IGF-BP\(\_1\),) were significant predictors of the risk of developing cancer of the prostate (Chan et al. 1998) and colon (Ma et al. 1999). More recently, we found in the New York Women's Health Study that high levels of c-peptide, a serum marker of insulin excretion, were strongly associated with the risk of developing colon cancer (Kaaks et al. 2000).

These results on endogenous hormones and anthropometry indicate that the relationship between diet and cancer is much more complex than was previously thought. Research on diet and cancer based solely on simple dietary questionnaire measurements and mainly retrospective case-control studies has led to the identification of some major dietary patterns associated with cancer risk (particularly the balance among vegetables, fruits and meat). Although these results are sufficient to support some broad and nowadays widely accepted dietary recommendations, cancer prevention would benefit from a better understanding of the biological links between diet and cancer. Laboratory investigations on human subjects combined with sound prospective epidemiologic projects should lead us a step further. This was the strategic choice made by the International Agency for Research on Cancer (IARC) when it decided 10 years ago to give priority in nutrition and cancer studies to the development of prospective cohort studies with repositories of blood samples collected from healthy study subjects (Coughlan 1991). We present here the major developments of the research strategy that led to the realization of the European Prospective Investigation into Cancer and Nutrition (EPIC).

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\(^3\) Abbreviations used: BP, binding protein; EPIC, European Prospective Investigation into Cancer and Nutrition; IARC, International Agency for Research on Cancer; IGF, insulin-like growth factor; SHBG, sex hormone binding globulin.
tions. In particular, a supplement of the International Journal of Epidemiology (Margetts et al. 1997) was devoted to the validity of different dietary assessment methods, questionnaires on physical activity and the reproducibility of anthropometric measurements. These studies provided precious information for the finalization of the study protocol. Three dietary methods were adopted on the basis of the results of these methodological studies conducted in 1990–1992:

- An extensive self-administered dietary questionnaire, which can provide data on up to 300–350 food items per country. This method was used in seven countries.
- An interview-based dietary questionnaire, very similar in content to the above but administered by direct computerized interview. This method was used in Spain and in Sicily (Ragusa) to increase compliance.
- A food-frequency questionnaire combined with a 7-d record. This method was adopted by the two centers in England.

In addition to the above dietary measurements obtained from all study subjects, it was decided to implement in EPIC a novel methodological approach to calibrate dietary measurements across countries to correct for systematic over- or underestimation of dietary intakes. For this purpose, a second dietary measurement was taken from an 8–10% random sample of the cohort by using a computerized 24-h diet recall method developed ad hoc (Slimani et al. 1999, Voss et al. 1998). We developed statistical methods to correct for bias in relative risk estimates that were due to systematic measurement errors in the baseline questionnaire, thereby making the cohort-specific estimates more comparable among study centers (Kaaks et al. 1994, Kaaks and Riboli 1997).

Although this general protocol was common to all EPIC centers, the procedure for storage of blood samples differed between two groups of countries because the study was originally started in seven European countries (France, Germany, Greece, Italy, Netherlands, Spain and United Kingdom) in which the study followed as strictly as possible a common, jointly elaborated protocol. Aliquots of blood samples collected from subjects from these seven countries were stored in 28 plastic straws (12 plasma, 8 serum, 4 erythrocytes, 4 buffy coat for DNA) and then split into two sets of 14 straws each. One set was stored locally and one was shipped to IARC to be stored in liquid nitrogen at −196°C in the central biological bank. Later, four additional study centers located in Sweden (Malmö and Umeå) and two in Denmark (Copenhagen and Aarhus) joined EPIC as associated projects. The two Swedish cohorts had been started before EPIC and the Danish ones had been started in parallel with EPIC. Their protocols and questionnaires (Kaaks et al. 1995a, 1995b), 24-h diet recalls were collected on a subsample of 33,200 subjects, corresponding to ~7% of the cohort. The age distribution of the calibration sample was designed to be as close as possible to the age distribution of the expected cancer cases during the first 10 y of follow-up.

These results will endow EPIC with an unusually large power to study the various cancer risk factors of interest. In fact, over 22,000 cases of cancer are expected to occur in the EPIC cohorts during the first 10 y of follow-up (by 2005).

Tables 2 and 3 provide the expected number of cancer cases by cancer site and country, expected to have occurred up to the end of 1998.

**Follow-up for changes in lifestyle and health conditions and for cancer incidence and mortality.** In EPIC, cohort members are contacted 3–4 y after recruitment to obtain information on some aspects of lifestyle that are known to be strongly suspected of being related to cancer risk, e.g., tobacco smoking, alcohol drinking, physical activity, weight, menstruation, pregnancies or menopause. In addition, a series of questions was added concerning whether the subjects had suffered from any major diseases. The first run of individual follow-up is on-going at present in most EPIC centers and has been completed in a few centers.

Follow-up aimed at the identification of cancer cases occurring among the EPIC cohort is based on population cancer registries and active follow-up through study subjects and their next of kin in three countries (France, Germany and Greece). Mortality data are also collected from either the cancer registry or mortality registries at the national level.

A working group created in 1996 (End-point Committee) prepared a detailed protocol for the collection and standardization of clinical and pathological data on each cancer site—Guidelines for Collection of End-point Data in the EPIC Study (IARC, unpublished, 1998). The document is available from IARC upon request. Currently, follow-up is being completed up to 31 December 1998. A delay of at least 18–24 mo in obtaining complete follow-up data is unavoidable because of the complex procedures followed by population-based cancer registries for the collection and verification of clinical and pathological diagnoses. On the other hand, these procedures provide complete and reliable follow-up data.

**TABLE 1**

<table>
<thead>
<tr>
<th>Subjects included in the study with Questionnaire</th>
<th>Blood collection</th>
<th>Completion of subject recruitment</th>
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</thead>
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<tr>
<td>Spain</td>
<td>41,446</td>
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<tr>
<td>Italy</td>
<td>53,097</td>
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</tr>
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<td>43,430</td>
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<td>Netherlands</td>
<td>40,110</td>
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<tr>
<td>France</td>
<td>69,321</td>
<td>24,371</td>
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<tr>
<td>Germany</td>
<td>53,130</td>
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<tr>
<td>Greece</td>
<td>27,883</td>
<td>28,632</td>
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<td>Sweden</td>
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<td>Denmark</td>
<td>57,054</td>
<td>56,800</td>
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<td>Total</td>
<td>484,042</td>
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SUMMARY

Epidemiologic studies on nutrition and cancer have provided strong evidence that dietary patterns, anthropometric characteristics and physical activity play an important role in the etiology of some of the most common cancers. Currently, public health recommendations generally promote the consumption of vegetables and fruits and advise moderation in the consumption of meat and salty foods. Although these general recommendations are justified by the current state-of-the-art situations, recent studies on metabolic factors (hormones and biomarkers of diet) suggest that the relation between nutrition and cancer is probably much more complex and involves various lifestyle factors in addition to single dietary composition. Most epidemiologic studies conducted to date were limited by the fact that they covered single and relatively homogeneous populations with limited variations in dietary habits.

TABLE 2

Number of cancer cases expected to have occurred in women in the European Prospective Investigation into Cancer and Nutrition (EPIC) up to the end of 1998 and made known to the International Agency for Research on Cancer (IARC) by the end of 1999

<table>
<thead>
<tr>
<th>Country</th>
<th>Center</th>
<th>Stomach</th>
<th>Colon-rectum</th>
<th>Lung</th>
<th>Breast</th>
<th>Cervix uteri</th>
<th>Corpus uteri</th>
<th>All sites but 173</th>
</tr>
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<tr>
<td>France</td>
<td>Paris</td>
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<td>138</td>
<td>45</td>
<td>521</td>
<td>74</td>
<td>99</td>
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<td>Italy</td>
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<td>17</td>
<td>7</td>
<td>49</td>
<td>4</td>
<td>10</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Varese</td>
<td>6</td>
<td>17</td>
<td>6</td>
<td>60</td>
<td>5</td>
<td>10</td>
<td>154</td>
</tr>
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<td>1</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>20</td>
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<td></td>
<td>Turin</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>19</td>
<td>2</td>
<td>3</td>
<td>50</td>
</tr>
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<td>Spain</td>
<td>Oviedo</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>23</td>
<td>5</td>
<td>6</td>
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<td>26</td>
<td>2</td>
<td>5</td>
<td>61</td>
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<tr>
<td></td>
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<td>1</td>
<td>19</td>
<td>3</td>
<td>4</td>
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</tr>
<tr>
<td>UK</td>
<td>Cambridge</td>
<td>8</td>
<td>40</td>
<td>35</td>
<td>111</td>
<td>9</td>
<td>17</td>
<td>333</td>
</tr>
<tr>
<td></td>
<td>Oxford</td>
<td>6</td>
<td>31</td>
<td>28</td>
<td>131</td>
<td>15</td>
<td>15</td>
<td>332</td>
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<td>Netherlands</td>
<td>Bilthoven</td>
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<td>11</td>
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<td>5</td>
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<td>7</td>
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<td>43</td>
<td>6</td>
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<td>142</td>
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<tr>
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<td>44</td>
<td>50</td>
<td>117</td>
<td>17</td>
<td>29</td>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td>107</td>
<td>499</td>
<td>280</td>
<td>1683</td>
<td>195</td>
<td>315</td>
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</table>

TABLE 3

Number of cancer cases expected to have occurred in men in the European Prospective Investigation into Cancer and Nutrition (EPIC) up to the end of 1998 and made known to the International Agency for Research on Cancer (IARC) by the end of 1999

<table>
<thead>
<tr>
<th>Country</th>
<th>Center</th>
<th>Stomach</th>
<th>Colon-rectum</th>
<th>Lung</th>
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<td>297</td>
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and were based solely on information provided by the study subjects through questionnaires.

The EPIC study was designed to overcome these two limitations. First, EPIC includes populations with important variations in dietary intake, particularly of vegetables and fruit. Second, with the collection and storage of blood samples, EPIC can provide the material for investigating various nutrition-related metabolic and genetic factors and their possible interactions.

**LITERATURE CITED**


## APPENDIX

Researchers and institutes collaborating in the European Prospective Investigation into Cancer and Nutrition (EPIC)

<table>
<thead>
<tr>
<th>Coordination</th>
<th>Location</th>
<th>Institute/Agency</th>
<th>Collaborators</th>
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<tr>
<td>Lyon</td>
<td>International Agency for Research on Cancer (IARC)</td>
<td>Elio Riboli, Rodolfo Saracci, Rudolf Kaaks, Nadia Slimani, Anne Linda Van Kappel, U Ruth Charrondiere, Bertrand Hemon, Corinne Casagrande, Françoise Clavel, Catherine GubOUT</td>
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</tr>
<tr>
<td>Paris</td>
<td>National Institute for Health &amp; Medical Research (INSERM), Institut Gustave Roussy</td>
<td>Anthony B. Miller, Jürgen Wahrendorf, Nikolaus Becker, Heiner Boeimg, Anja Kroke, Manuela Bergmann, Andro Jeckel</td>
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<td>Institute of Epidemiology and Social Medicine, University of Aarhus</td>
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<td>Barcelona</td>
<td>Catalan Institute of Oncology (ICO)</td>
<td>Carlos González, Antonio Agudo, Silvia Argilaga, Carmen Martínez, Mauricio Rodríguez, J. Ramón Quiros, Cristina Lasheras, Miren Dorronsoro, Pilar Amiano, José M. Begiristain, Carmen Navarro, Maria D. Chirlaque, Maria J. Torno, Aurelio Barricarte, Eva Ardanz</td>
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