In what was originally considered the Western world, lung cancer is among the most frequently occurring cancers, particularly in men. In the period 1988–1992, the incidence in men ranged from 99 per 100,000 per year in US Blacks to 24 per 100,000 per year in Sweden [1]. In women, however, the incidence is usually lower (ranging from 39 in US Blacks to 3 in Spain), but in contrast to the male incidence it is still expected to increase in the near future. As we all know, lung cancer incidence reflects cigarette-smoking habits with a lag time of about 20–30 years [2].

Although smoking is by far the most important cause of lung cancer, responsible for approximately 90% of the lung cancer incidence, this knowledge is only 50 years old. At that time, independent of each other, two case-control studies were published in the US and England which demonstrated a strong association between cigarette smoking and the risk of lung cancer [3, 4]. Unfortunately, almost no one, besides the investigators themselves, wanted to believe that the association was causal. Even after publication of the famous study by Doll and Hill [5], a prospective cohort study among more than 40,000 British doctors confirming the results of the previous case-control studies, it took many years before the public at large (and their governments) took their results seriously. Also passive smoking increases the risk for lung cancer by 20–30% [2].

Other proven risk factors for lung cancer include mainly occupational exposures, such as ionizing radiation, several types of mining (arsenic, uranium) and asbestos [2]. Although occupational risk factors may be strong, they account only for a small proportion of all lung cancer cases (estimated at about 10%), because,
in contrast to smoking, only a small proportion of the population has been exposed to them. Whether air pollution is a significant risk factor for lung cancer remains to be proven.

Of all the frequently occurring cancers, lung cancer was the only one for which most of the causes were thought to be known. It was not until 25 years ago that some evidence was produced showing that lung cancer risk in humans may also be influenced by nutritional status.

**Diet and Nutritional Status**

An extensive and excellent review on nutrition and lung cancer has been given by Ziegler et al. [6]. Therefore, the studies included in that review will not be discussed in detail here, except if they provided key evidence with respect to the diet and lung cancer association. The chemoprevention trials for lung cancer will also not be discussed in detail, since they are the subject of another chapter in this volume.

*Carotenoids and Other Micronutrients, and Vegetables and Fruits*

The first studies focused on vitamin A, the combination of preformed vitamin A (retinol) and provitamin A carotenoids, of which β-carotene, present in many vegetables, is the most important representative [7–9]. These studies observed strong inverse associations with dietary vitamin A intake. Two other early studies found inverse associations with vegetables, in particular green leafy [10] or yellow-green vegetables [11]. An article by Peto et al. [12] suggested that β-carotene, which has antioxidant properties, might be a cancer-protective substance and this article set the research agenda for diet, chemoprevention and cancer for the next 10 years. Numerous case-control studies and a considerable number of prospective cohort studies have been conducted since then, not only investigating dietary intake, but also blood levels of β-carotene. Ziegler et al. [6] concluded that all eight cohort studies and almost all case-control studies observed a reduced lung cancer risk at high levels of vegetable and/or fruit consumption, or at high intake of carotenoids or vitamin C. Also blood levels of β-carotene, based on frozen blood samples stored at temperatures lower than –20°C, showed consistently inverse associations with lung cancer risk in six of seven prospective studies [13], even though the number of subjects in these studies mostly did not exceed 100.

In their famous review from 1991, Steinmetz and Potter [14] were among the first to shift the attention from the well-known and frequently investigated micronutrients, such as β-carotene and vitamin C, to their sources, i.e. vegetable and fruits. They concluded that for lung cancer the evidence for a protective effect of vegetables and fruits was most conclusive. It also became clear that the consistent inverse associations for β-carotene and/or vitamin C might be due only to their
Table 1. Prospective cohort studies on vegetables and fruits, and intake of selected micronutrients

<table>
<thead>
<tr>
<th>Year</th>
<th>Location population</th>
<th>Ref.</th>
<th>Sex</th>
<th>No. of cases</th>
<th>Years of follow-up</th>
<th>Dietary assessment</th>
<th>Smoking adjustment</th>
<th>Vegetables</th>
<th>Fruits</th>
<th>Carotenoids</th>
<th>Retinol</th>
<th>Vitamin A</th>
<th>Vitamin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>USA (Ill.)</td>
<td>44</td>
<td>M</td>
<td>33</td>
<td>19</td>
<td>DH</td>
<td>–</td>
<td>↓↓</td>
<td>–</td>
<td>–</td>
<td>↑↑</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1983</td>
<td>Norway</td>
<td>8</td>
<td>M</td>
<td>81</td>
<td>9–12</td>
<td>FFQ</td>
<td>±</td>
<td>↓</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1986</td>
<td>Japan</td>
<td>45</td>
<td>M</td>
<td>1,454</td>
<td>17</td>
<td>FFQ</td>
<td>±</td>
<td>↓↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F 463</td>
<td>(1 item)</td>
<td></td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1987</td>
<td>Netherlands</td>
<td>46</td>
<td>M</td>
<td>63</td>
<td>25</td>
<td>DH</td>
<td>+</td>
<td>–</td>
<td>↓↓</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1992</td>
<td>USA (Calif.)</td>
<td>47</td>
<td>M</td>
<td>125</td>
<td>8</td>
<td>FFQ</td>
<td>+</td>
<td>↑↑</td>
<td>↑</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F 70</td>
<td></td>
<td></td>
<td>+</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1991</td>
<td>USA (7th-D. Adv.)</td>
<td>48</td>
<td>M</td>
<td>61</td>
<td>6</td>
<td>FFQ</td>
<td>+</td>
<td>↑↑</td>
<td>↓↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1991</td>
<td>Finland (smokers)</td>
<td>24</td>
<td>M</td>
<td>93</td>
<td>14–20</td>
<td>DH</td>
<td>±</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>↓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1992</td>
<td>USA (Lutherans)</td>
<td>49</td>
<td>M</td>
<td>219</td>
<td>20</td>
<td>FFQ</td>
<td>+</td>
<td>0</td>
<td>↓</td>
<td>↓</td>
<td>0</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>1993</td>
<td>USA (Iowa)</td>
<td>21</td>
<td>F</td>
<td>138</td>
<td>4</td>
<td>FFQ</td>
<td>+</td>
<td>↓↓</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1996</td>
<td>UK (Wales)</td>
<td>15</td>
<td>M</td>
<td>51</td>
<td>13.8</td>
<td>FFQ</td>
<td>±</td>
<td>0</td>
<td>↓</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>↑↑</td>
</tr>
<tr>
<td>1997</td>
<td>USA (NHEFS)</td>
<td>16</td>
<td>M</td>
<td>248</td>
<td>19</td>
<td>24h/FFQ</td>
<td>+</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1997</td>
<td>USA (N.Y.)</td>
<td>17</td>
<td>M</td>
<td>395</td>
<td>7</td>
<td>FFQ</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>↓↓</td>
<td>↓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F 130</td>
<td></td>
<td></td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1999</td>
<td>USA (nurses)</td>
<td>18</td>
<td>F</td>
<td>593</td>
<td>16</td>
<td>FFQ</td>
<td>+</td>
<td>↓*</td>
<td>↓*</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>↑**</td>
</tr>
<tr>
<td>2000</td>
<td>Netherlands</td>
<td>19</td>
<td>M</td>
<td>939</td>
<td>6.3</td>
<td>FFQ</td>
<td>+</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F 135</td>
<td></td>
<td></td>
<td>0</td>
<td>↓↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* No data on total vegetable and fruit consumption available.
** Intake including that from supplements.

association with vegetable and fruit consumption, in other words they might be indicators for vegetable and fruit consumption without having any causal relationship with lung cancer.

Since in the area of dietary studies, prospective cohort studies are less prone to some biases than retrospective case-control studies (see below), a closer look at the cohort studies is warranted. Since the review by Ziegler et al. [6], results of a number of other cohort studies relevant to this issue have been published [15–20]. The 14 prospective studies in Table 1 and in Figures 1 and 2 illustrate very clearly that the evidence for a protective effect of vegetables and fruits and carotenoids and vitamin C is quite consistent, although there are a few exceptions. (One such exception is the very small Caerphilly study, in which no association was found for vegetables and a weakly inverse association for fruit. In contradiction with the latter finding, a positive association was observed for vitamin C [15]). Ziegler et al. [6], however, concluded that the evidence for vitamin C is not convincing, but as far as the cohort studies are concerned this conclusion does not seem to be
Fig. 1. Rate ratios and 95% confidence intervals (highest vs. lowest category) of dietary intake of carotenoids or β-carotene and lung cancer in prospective cohort studies (□ = males, ○ = females).

Fig. 2. Rate ratios and 95% confidence intervals (highest vs. lowest category) of dietary intake of vitamin C and lung cancer in prospective cohort studies (□ = males, ○ = females).
justified, since the inverse associations of vitamin C with lung cancer risk are as consistent as those for β-carotene (Table 1; Fig. 1, 2).

Some of the studies indicate that indeed associations for vegetables are stronger than for β-carotene, lending support to the idea that β-carotene is only an indicator of vegetable consumption [6, 21]. There is some indication that the evidence for fruit is somewhat stronger than for vegetables, at least in the cohort studies (Table 1). No clear evidence for particularly effective types of vegetables and fruits can be obtained from the studies, but this may also be due to the large variation between the studies in dietary patterns, food frequency questionnaires and data analysis. Verhoeven et al. [22] screened studies on brassica vegetables, a genus of the cruciferous family, and concluded that all lung cancer studies with available data on consumption of brassicas (two cohort studies and nine case-control studies) observed an inverse association for one or more specific brassicas and only two studies also found a positive association. Although these results seem promising, it should be kept in mind that the studies did not indicate whether the effects are attributable to brassicas per se or to vegetables in general. Our study, the Netherlands Cohort Study in which all regularly eaten vegetables were investigated, is more supportive of a general vegetable effect [19]. For fruits, there are tendencies showing that citrus fruits are more effective than other types of fruit, but for the reasons described earlier it is not yet possible to draw any firm conclusions.

If indeed vegetables and/or fruits are effective against lung cancer and β-carotene and/or vitamin C are not, what is it that makes them effective? Are there a few other bioactive substances in vegetables and fruits or is it the matrix itself in which all components together are required for the effect? Surprisingly, only a few other micronutrients have been investigated in a minority of the studies to date. Other micronutrients with antioxidant properties include vitamin E. According to Ziegler et al. [6], the evidence for a protective effect of vitamin E is not convincing, whereas the report of the World Cancer Research Fund concludes that vitamin E possibly decreases the risk of lung cancer [23]. In our cohort study we did not observe any association for vitamin E [20], nor did any of the other cohort studies that included this nutrient [16–18, 24, 25].

After good food composition tables on carotenoids became available, a few studies also investigated other carotenoids, such as lutein (+zeaxanthin), lycopene and β-cryptoxanthin. Lutein (an antioxidant that has no vitamin A activity) and α-carotene were also found to be protective in two of the three case-control studies [26, 27], but not lycopene and β-cryptoxanthin. In the third case-control study in women, in which estimates for carotenoids were presented after adjustment for vitamin C and E intake, lutein (weakly), α-carotene and lycopene were inversely associated with lung cancer risk besides β-carotene [28]. In a prospective, nested case-control study on specific carotenoids in blood, lutein and β-cryptoxanthin, besides β-carotene, were also found to be lower in lung cancer cases [29]. In the Nurses’ Health Study, including 593 female lung cancer patients, no association
was observed for dietary intake of lutein, a statistically significant inverse association for \( \alpha \)-carotene, and statistically nonsignificant inverse associations for \( \beta \)-carotene, \( \beta \)-cryptoxanthin, and lycopene [18]. In our cohort study, including 939 male patients, of all the carotenoids we observed the strongest inverse associations for dietary intake of lutein (+zeaxanthin) and \( \beta \)-cryptoxanthin [20]. Altogether, no clear picture with respect to specific carotenoids arises from these results, which are nevertheless consistent with a protective effect of vegetables and fruits.

Another hardly investigated but interesting compound with respect to carcinogenesis is folate. Although folate has mainly been connected to a reduced risk of colorectal cancer, there is no real reason why it should not have a function with respect to other cancers, since folic acid is involved in the synthesis of DNA. A relative deficiency might therefore interfere with normal cell replication. To date, three cohort studies (one in men and women, one in women only, and one in men only) [17, 18, 20], and two case-control studies [30, 31] have been conducted on dietary folate intake and lung cancer risk. Whereas the case-control studies did not find an association, two of the cohort studies observed an inverse association [17, 20]. Both cohort studies found somewhat stronger inverse associations for vitamin C and folate than for specific carotenoids, in particular among the men. In the latter study, an attempt was made to disentangle the effects of folate and vitamin C from those of the carotenoids. After adjustment for folate and vitamin C, the inverse associations for specific carotenoids disappeared, whereas those for folate and vitamin C remained strong [20]. No association was observed in the Nurses' Health Study, but in this study the intake of folate included the intake from supplements [18].

Other bioactive substances in vegetables and fruits include flavonoids and glucosinolates. Glucosinolates and their enzymatic hydrolysis products, such as isothiocyanates and indoles, are prevalent in cruciferous vegetables, including vegetables of the brassica genus. In experimental studies, these substances have been shown to be anticarcinogenic. They are able to influence phase 1 and phase 2 biotransformation enzyme activities, thereby possibly influencing several processes related to chemical carcinogenesis, e.g. metabolism, DNA binding and mutagenic activity of promutagens [32]. No epidemiologic studies have been done to study their effects in humans, although some experimental research in humans suggests that brassicas, in particular brussels sprouts, produce less DNA damage and more induction of glutathione S-transferase [33]. From the observation that brassica vegetables seem to exert a protective effect, we might conclude that glucosinolates and their breakdown products are effective [22]. However, too many links are still missing in this area of research to draw any firm conclusions yet.

Flavonols and flavones constituents of many plant foods (onions, tea, apples and vegetables) and considered as rather strong antioxidants, were recently investigated in several epidemiological studies. No effect on lung cancer was observed
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...in two Dutch cohort studies [34, 35]. In a Spanish case-control study, no consistent association was shown [28]. Only a Finnish cohort study observed an inverse association, which remained after adjustment for antioxidant vitamins [36]. A wide range in the intake of flavonols and flavones (all calculated with the same analytic figures) was seen between the studies: low in Finland and Spain (4–6 mg/day), but much higher in the Netherlands (27 mg/day). Black and green tea are not only important sources of flavonols but also of catechins (another type of flavonoids). Numerous epidemiological studies, however, have not consistently shown a protective effect for tea [37].

Apart from stratification according to gender, a number of studies have investigated other subgroups in the population, i.e. subgroups divided according to smoking status and according to tumor histology. Most of the evidence on the effects of vegetables and fruits is derived from former and current smokers, as these groups contribute to almost all the lung cancer cases. Never-smokers are too few in number in most studies to yield sufficiently precise estimates. Several studies, however, focused specifically on non-smokers. Ziegler et al. [6] concluded that the effects in never-smokers are of the same magnitude as those in smokers.

As far as histologic subtype is concerned, no distinct differences in effects of vegetables and fruits have been observed [6], although there are some indications that for adenocarcinoma, a type of tumor less strongly related to smoking, the effect is somewhat weaker [19].

**Selenium**

Several prospective cohort studies have been conducted on blood or toenail selenium levels and lung cancer risk; assessment of dietary intake is unreliable. The only studies that observed strong inverse associations were done in Finland (blood) and the Netherlands (toenails). Both countries have low to medium levels of selenium in the soil and therefore in a large part of the food supply. Nevertheless, the evidence for a protective effect of selenium was not considered sufficiently convincing [6].

**Fat Intake and Meat Consumption**

The hypothesis that fat may be related to lung cancer risk came from ecological studies which showed consistent positive associations with lung cancer mortality, even after adjustment for smoking. Up to 1996, five case-control and four cohort studies (with relatively small numbers of cases) had been conducted on dietary fat and lung cancer risk. They either found no or a modest positive association of lung cancer risk with total and saturated fat and cholesterol, with the exception of one case-control study among non-smoking women which observed a strong risk for saturated fat [6]. Since then, several other studies have been published. In men, the New York State Cohort Study observed modest positive associations for total, monounsaturated and saturated fat, but not for cholesterol [17]. In women, however, these associations were not confirmed; saturated fat even showed an...
inverse association. Another cohort study among Norwegian men and women found no association with dietary cholesterol and saturated fat and an increased risk for mono- and polyunsaturated fat. Cod liver oil supplementation was associated with a strongly decreased risk [38]. The Nurses’ Health Study observed no associations for total fat and most types of fatty acids including trans fatty acids, a statistically nonsignificant weak inverse association for vegetable fat and linoleic acid, and a statistically significant positive association for cholesterol [18]. The results of these studies taken together appear to be very inconsistent with respect to the association between the intake of fat and fat types and the risk of lung cancer.

Sinha et al. [39] looked at associations with meat and well-done meat in a large and sophisticated case-control study among women. Fried, well-done meat contains high levels of carcinogenic heterocyclic amines. All meat and red meat, except not-well done and not-fried red meat, showed statistically significantly increased risks for lung cancer.

**Alcohol**

Quite a number of studies on alcohol consumption and lung cancer risk have been published to date [23]. As alcohol consumption is strongly related to smoking, the debate has always been whether the positive association observed in many studies is due to residual confounding by smoking (see below). Recent cohort studies that adjusted extensively for smoking included the New York State Cohort, which observed no association for total alcohol [17]. Two recent cohort studies that also evaluated type of alcoholic beverage were done in Finland (ATBC trial cohort) and Denmark. Total alcohol consumption was not related to lung cancer in the Finnish study, nor were any of the beverage types [40]. The category with the highest alcohol intake corresponded to a consumption of about 4 drinks/day. The Danish study showed a modestly increasing risk in men starting at a level of more than 3 drinks/day [41]. Since women did not drink such amounts, this association could not be evaluated in women. Simultaneous inclusion of all beverage types in the multivariate model revealed a positive association for beer and a strongly inverse association for wine, both in men and women, but for spirits a positive association in men and an inverse one in women.

We can conclude from the evidence that the question whether alcohol enhances lung cancer is still unresolved, but it is very unlikely that an effect, if any, is large.

Summarizing all the evidence on dietary factors and lung cancer risk, we conclude that only for vegetable and fruit consumption the evidence appears to be reasonably consistent. But, as almost all the evidence is based on observational studies, a number of methodological considerations will influence the final conclusion.
Methodological Issues

Several methodological issues are to be kept in mind when single observational studies or an entire set of studies are being evaluated. Besides issues as selection and recall bias, nutritional epidemiology is further complicated by measurement problems and multicollinearity of the diet. Finally, we have to realize that smoking is by far the most important determinant of lung cancer (except for some occupational exposures) and smoking can therefore confound the associations of dietary variables with lung cancer risk. In the following we will discuss if and how inference from the consistently observed protective effects of high vegetable and fruit consumption may be influenced by methodological issues.

Biases

One of the less obvious biases is publication bias, not only introduced by journals as is often thought, but also by authors themselves. In observational epidemiology, it can even play a role in submission of grant proposals and selection of PhD projects: if preliminary data analysis does not show something ‘interesting’, a project might not be undertaken. The result of this bias is that studies with negative results tend to be published less. Although publication bias will almost certainly have played a role in the set of evidence on diet and lung cancer, it is unlikely that it entirely explains the consistent protective effects of vegetable and fruit consumption shown in so many studies.

Other, well-known potential biases include selection and recall bias. Both types of bias may affect retrospective case-control studies more than cohort studies. Selection bias arises in a case-control study if cases and controls are not comparable. Recall bias occurs if cases, due to their disease, recall their diet in the period before diagnosis differently than controls. The difficulty is, however, to evaluate for a specific study whether these biases have played a role. Low response rates in cases and/or controls or a bad selection of the control group may give some indication on the possible presence of selection bias. The presence of recall bias is even more difficult to assess, although some studies have investigated this issue with varying results and not with respect to lung cancer. For this reason, the evidence from prospective cohort studies, in particular in the area of diet and cancer, is usually weighted more heavily than the evidence from case-control studies.

A type of bias related to recall bias, which may play a role in both types of study design, is the “presence of disease” bias: even before diagnosis, the dietary pattern of a case-to-be may be influenced consciously or unconsciously by (subclinical) symptoms of the disease. Thus, although dietary habits may be reported correctly, they may nevertheless be influenced by disease status. In cohort studies such a bias is often evaluated by excluding cases diagnosed in the first or first 2 years of follow-up. In cohort studies on gastrointestinal cancers, where such a bias is much more plausible than in lung cancer, this exclusion should be and mostly is common practice. We have shown that such a bias may exist with respect to vegetable
consumption and stomach cancer risk [42]. In case-control studies, the presence of disease bias is much more difficult to evaluate.

With respect to vegetables, fruits and lung cancer, a large effect of these biases is not very likely also because the majority of prospective studies have shown the same protective effects as case-control studies.

Measurement Error

Assessment of dietary intake is notoriously difficult. Because they are easy to administer, most studies have used food frequency questionnaires (FFQs) with a large range in the number of items included. Some FFQs are specially developed to achieve a good rank ordering of study subjects with respect to the intake of specific nutrients. Rank ordering is a requirement for epidemiological studies, more than correct assessment of absolute intake. Nevertheless, validation studies have shown that even the best questionnaires measure dietary intake with error. The maximum obtainable correlation coefficients between the FFQ and reference method (often a many-day dietary record) are in the order of 0.7 to 0.75 (also dependent upon the type of nutrient and its distribution across foods). A number of validation studies have shown that correlation coefficients for total vegetable consumption amount to only 0.4, whereas assessment of total fruit consumption is somewhat better. Altogether, the presence of measurement error implies that the strength of any true association between vegetable and fruit consumption and lung cancer is underestimated.

Residual Confounding by Smoking

Smoking is not only a strong determinant of lung cancer risk, many studies have also shown that smokers, in particular current smokers, tend to have less ‘healthy’ dietary habits [43]. For example, they eat less vegetables and particularly less fruit. It has also been shown that smokers have lower levels of several antioxidants in their blood, even if they have similar intakes. It seems that smoking depletes the antioxidant pool in the body. Confounding by smoking therefore endangers the interpretation of the diet and lung cancer association. All the studies in this review have adjusted for smoking habits. Nevertheless, not all studies have detailed smoking data available or have tested and used the most optimal adjustment for smoking. Adjustment for the following smoking variables is minimally required: number of cigarettes per day, duration of smoking and smoking status (current or former). Although most studies have adjusted for these or comparable variables, we cannot entirely exclude residual confounding by smoking in the complete set of evidence on vegetable and fruit consumption. This implies that the effect may have been overestimated in some or all the studies. Future research and more detailed data analysis in existing data sets (e.g. sensitivity analysis) might shed more light on this issue.
Multicollinearity of Dietary Variables

A dietary pattern is a very complicated concept to assess, since the intake of foods, nutrients and other constituents of the diet are not independent. Some nutrients show very high correlations, most often because they share the same food sources (e.g. β-carotene and vitamin C), but also because their food sources are positively or negatively associated in a dietary pattern (e.g. people who eat a lot of savory snacks, eat less fruit). Subjects with a high consumption of fruits or juice usually have a high intake of vitamin C, etc. This complexity makes it difficult to decide which of the factors represent potential causal factors and which factors are only indicators of other, more important factors. Although sophisticated data analysis can certainly help to guide these decisions, other types of research (e.g. intervention studies) are required to really obtain the final proof.

Conclusion

In summary, we conclude that the only potentially causal dietary link with lung cancer to date appears to be vegetable and fruit consumption, without definitely knowing which constituents are responsible for this effect. We do not know for sure the magnitude of the effect: whereas measurement error underestimates the association, several biases and residual confounding can overestimate the association. The net effect can therefore not be estimated accurately at present.

Despite all these limitations, we made an attempt to estimate the impact of vegetable consumption on lung cancer risk based on data from the Netherlands Cohort Study on Diet and Cancer [19]: a male, current smoker who has smoked 25 cigarettes/day for 40 years has a risk of attracting lung cancer that is 16 times as high as that of a never-smoker. By eating 286 g of vegetables/day (highest quintile) instead of 103 g (lowest quintile), he may reduce his risk by 19% and by eating 325 g/day of fruits (highest quintile) instead of 46 g/day (lowest quintile) he may reduce his risk by 31%. If the whole (male) population increased its vegetable consumption up to the highest level, 13% of all lung cancers could be prevented. Although this percentage is low in comparison with not smoking, which prevents 90% of all lung cancers, it is still worthwhile.

References

Epidemiology of Nutrition and Lung Cancer


**Discussion**

Dr. Ottery: I liked your first three-dimensional graphic very much. I am interested in your interpretation of the ‘blip’ where the relative risk went up to 1.15. Was this real or just a blip on the graphic? Was there something in the interrelationship of the fruit and vegetables that caused them to counteract each other?
Dr. Goldbohm: It was real. That’s what happens in this type of epidemiological study. I think it’s mainly a matter of chance. The ranges of exposure that you study are not very large and we were looking at quite small differences. There are lots of reasons why there might be deviation from a nice line. When I see an epidemiological study with a very perfect dose-response association, I get suspicious, because I don’t think it works like that in epidemiology.

Dr. Ottery: Speaking as a clinician, I think one has to be very careful in looking at long-term nutrient intake, say 1–6 years after a diagnosis of lung cancer or stomach cancer. Most people who have those two diseases have died within the first year or within the first couple of years, so the people who survive for 3 or 6 years may have no resemblance to your total cohort in terms of their intakes. And in that first year, if they are undergoing chemotherapy, radiation, and so on, their intake may be quite at variance with what they might want to take in or with what they may actually be absorbing.

Dr. Goldbohm: A very good point. This emphasizes one of the problems of case-control studies, especially with diet. In such studies the patients have already been diagnosed with the disease when they are asked about their dietary intake before diagnosis, and their responses may well be influenced by their knowledge of the diagnosis. They are looking for causes, and their responses will reflect that. Unfortunately in nutritional epidemiology, case-control studies may be necessary because there is no better alternative, but prospective cohort studies are better because you have a baseline dietary assessment before the diagnosis, and thus before any treatment has been started. The subjects obviously don’t know yet that they’re going to get cancer a year or two later. But even with cohort studies you may find, in stomach cancer for example, that patients have already changed their dietary habits up to 2 or 3 years before diagnosis. So you have to take those effects into account and exclude the cases diagnosed in the first years of follow-up.

Dr. Pichard: I would like to know how confident you are about the precision of epidemiological data on food intake. For example, there are seasonal effects on food intake and we also all know that food questionnaires are quite inaccurate, by 20–30% or even more.

Dr. Goldbohm: That’s the issue of the measurement error that I showed you. We are not able to make precise measurements of dietary intake, and certainly not of vegetable intake. I think fruit is somewhat easier than vegetables because of problems with portion sizes, etc. In the best case what happens is that if there is a true association between vegetable consumption and lung cancer, then we underestimate that association and you may be able to correct for that. We know this happens. There’s clearly an underestimation of an effect of vegetable and fruit consumption owing to measurement error. But I don’t want to compromise the whole dietary assessment in epidemiology because for some kinds of study it’s the only thing we have, so it’s up to us to do it as well as possible. Epidemiologists are very good at showing how bad methods are, but the next step, of course, is to do something about it – to try to improve the method and to devise ways to correct for errors.

Dr. Riboli: As a general comment I would like to say that science is to a large extent a problem of measurement. Whether you are a nuclear physicist or a nutritional epidemiologist, your problem is to measure something which happens somewhere, and to find out whether what happens in case A is different from what happens in case B, whether you are measuring electrons or vitamin C. I think that epidemiologists are a little more aware of the problems of imprecision in measurement than, with all due respect, perhaps laboratory scientists, because we are closer to biostatistics in our training. So we see more directly what happens when you have imprecision. I would like to emphasize the difference between imprecision and bias, otherwise we may spend 3 days misunderstanding each other. Imprecision has nothing to do with systematic measurement error. Imprecision simply means that you sometimes measure a little bit too high, sometimes a little bit too low. The result is like what might happen in a clinical trial if you made an error and mixed a little bit of the placebo with the drug, or a little bit of the drug with the placebo; you end up by finding that the
difference between the treated group and the placebo group is not as strong as you would expect if you had not mixed up the pills, even if the drug is active. This is measurement error. Thus if a cohort contains a mixture of people who eat oranges and people who don’t each oranges then, if oranges are the factor that protects against lung cancer, you could find, because of the measurement error, that the effect was small when it should be large. This is the problem of dietary measurement and people working in the field are very much aware of it. If you have a systematic measurement error, where for example everyone who eats meat tells you they eat fish, then you have bias, and that’s a different problem.

**Dr. Baracos:** It strikes me as questionable, comparing your presentation with the previous one, to try to draw a parallel between someone eating a normal diet and someone taking a very highly modified diet containing purified antioxidants and phytochemicals. I wonder if the epidemiologists could give Dr. Hursting some recommendations for a dietary design based on natural ingredients or food substances that he could use to bring these two very widely separated approaches closer together.

**Dr. Goldbohm:** That, of course, is the ultimate goal of the whole field of nutrition and cancer investigation. In observational studies, you stick with what people do in real life. They don’t select foods on the basis of their nutrients or whether they are fortified or not – though perhaps in the USA they may do so by now – but in most populations people just choose their foods according to whether they like them or not. And one of the things that is happening now is that many studies are being done to analyze dietary patterns, so that at least gives us an idea of the general characteristics of the diet. But of course that’s not bridging the gap between the experimental studies and the epidemiological studies. The classic study design that does bridge that gap is the human intervention study. I showed the example of the famous ATBC trial [1], but many results are now coming in from colon cancer/polyp prevention trials with substances like fiber, calcium, and many other substances.

**Dr. Go:** I’d like to make a comment about bias. Food supply is in the process of change. The food marketplace is changing tremendously and the food industry is responding by producing foods specifically aimed to be good for health. So if you conduct studies over 5 or 10 years while the food supply is changing, this will introduce bias, which became very obvious to us in the Women’s Health Initiative. The other comment I would like to make is in relation to the question about how you jump from an epidemiological database to animal models of molecular interventions or mechanistic effects. These are very different things. What Dr. Hursting has shown us is an animal model with a defined dietary intake. His rodents are not normal, they are not rats running around free – they are confined to a cage, or to a defined environment, with temperature control, water control, everything else under control. His purpose in his studies is to look at a mechanistic event, to follow a certain event in multiple step carcinogenesis. To translate those data to human studies is a very large step, particularly when we consider what a long time it takes for intraepithelial neoplasia to develop in humans. This is why I think the key question for Dr. Hursting is whether he can adjust his animal model to be more relevant to humans, by allowing exercise, by changing the diet and making it less defined, and by using transgenic methodology to manipulate the model so that it becomes closer to the human situation.

**Reference**