European Consensus Statement on Lung Cancer: Risk Factors and Prevention

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Introduction

This article is based on the Hohenheim Consensus Meeting, which was the second in a series of World Health Organization (WHO) consensus conferences. Organized by WHO Europe and the German Ministry of Health and held at Hohenheim University, November 28–30, 1996, the Hohenheim Consensus Meeting included experts in the field of diet and cancer assigned to four panels corresponding to cancers of the lung, stomach, colon, and breast. Each panel focused on eight to ten questions that allowed panel members to discuss what is known and not known about diet and that particular cancer site and priorities for future research. The results of the discussion on lung cancer are reported here.

What Are the Known Key Factors That Increase the Individual Risk for Lung Cancer?

Smoking is the major risk factor, accounting for about 90% of lung cancer incidence. There are additional exogenous and endogenous factors contributing to the individual risk, such as the following:

- Low consumption of fruit and vegetables
- Genetic predisposition
- Exposure to non-tobacco procarcinogens, carcinogens, and tumor promoters
- Previous lung disease such as chronic obstructive pulmonary disease (COPD)
- Previous tobacco-related cancer
- Passive smoking

The increase of lung cancer mortality...
ty in the last decades can be entirely attributed to the trend of tobacco consumption.\textsuperscript{1,2} However, there is a lag time of many years between beginning smoking and the clinical manifestation of cancer. This fact may distort the perception of lung cancer risk factors by the individual. Moreover, the lag makes clinical intervention studies to reduce the cancer risk difficult to design and to interpret. Therefore, most of our current knowledge concerning lung cancer prevention in the human is based on observational studies.

**Low Consumption of Vegetables and Fruit**

A large number of observational studies all over the world have consistently found that increased consumption of vegetables and fruit is associated with a reduced lung cancer risk in smokers, ex-smokers, and never-smokers.\textsuperscript{3} However, the specific mechanisms of the epidemiological association between diet and lung cancer incidence remain to be elucidated. So far, no single dietary compound has been identified to exert a chemopreventive action on lung cancer. Thus, after quitting smoking, an increased vegetable and fruit consumption appears, for the present, the safest option to reduce lung cancer risk.

**Genetic Predisposition**

Individual lung cancer risk depends on both inherited and environmental factors. In the near future, improved understanding of the molecular genetics of lung cancer may have major implications for both risk assessment and prevention of lung cancer.\textsuperscript{4} Subjects with genetic predisposition might reduce their lung cancer risk by a proper intake of vegetables and fruit.

**Exposure to Non-Tobacco Carcinogens**

Exposure to radon, asbestos, and chemical carcinogens stimulates lung cancer development. The lung cancer risk from non-tobacco carcinogens is multiplicative with the risk increase from smoking.

**Previous Inflammatory Lung Disease**

Chronic inflammatory lung diseases, such as asthma, COPD, and tuberculosis, are associated with an increased lung cancer risk in later life. Possible explanations for the increased cancer risk from chronic inflammation are the mutagenic effect of free radicals produced by inflammatory cells and the stimulation of cell proliferation in tissue regeneration. In the National Health and Nutrition Examination Survey (NHANES) II study it was demonstrated that a low intake of vitamin A is associated with increased COPD risk.\textsuperscript{5}

**Previous Cancer**

Low intake of vitamin A might contribute to metaplastic changes in the respiratory mucosa.\textsuperscript{6} The increased risk for a secondary primary cancer at different sites of the body is explained by both genetic predisposition and the effect of an unhealthy lifestyle, such as smoking and low intake of vegetables and fruit.

**Passive Smoking**

Environmental tobacco smoke is to be considered as a human carcinogen. However, the extent of the lung cancer risk from passive smoking remains a fiercely discussed subject.\textsuperscript{7}

**Is There Convincing Epidemiological Evidence That Nutrition Is Involved in the Primary Prevention of Lung Carcinogenesis?**

Yes, there is consistent evidence from observational studies that high consumption of vegetables and fruit is associated with a lower risk. A recent review on nutrition and lung cancer concluded that “observational studies of diet and lung cancer, both prospective and retrospective, continue to suggest that increased vegetable and fruit intake is associated with re-
duced risk in men and women; in various countries; in smokers, ex-smokers, and never-smokers; and for all histologic types of lung cancer.”

The evidence was summarized as follows: “in all eight prospective and 18 of 20 retrospective studies, lung cancer risk was reduced at high levels of vegetable and/or fruit consumption, or at high intake of carotenoids or vitamin C, which are markers of vegetables and fruit intake.”

In the large-scale Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) and β-Carotene and Retinol Efficacy Trial (CARET) intervention studies, on the basis of 894 and 275 incident cases of lung cancer, respectively, those with higher pre-intervention serum or intake levels of β-carotene experienced a lower risk of lung cancer, providing further support for the evidence that vegetables and fruit may protect against the development of lung cancer.

In the ATBC, participants had to be male smokers of five or more cigarettes daily and 50 to 69 years of age. At study entry the 29,133 men who were randomized averaged about 36 years. Thus, the ATBC trial results further support the contention that even in long-term heavy smokers the consumption of vegetables and fruit reduces the risk of subsequent lung cancer. In the CARET study the reduction in risk was seen in current and, though not statistically significant, in former smokers as well.

Are There Specific Dietary Components (e.g., Vitamins, Trace Elements) That Play a Preventive Role in Human Lung Carcinogenesis?

At present, no single component of the diet has been identified that can replace the beneficial effect of high consumption of vegetables and fruit. However, evidence has accumulated that, presumably, the multiple components of the food may act in concert to produce the overall beneficial effect.

From epidemiological data there is evidence that β-carotene plasma levels are inversely correlated with lung cancer risk. Consequently, it is argued that a high intake of β-carotene–rich fruit and vegetables might be preventive against this type of cancer. From epidemiological results it can be concluded that β-carotene in plasma serves as a marker for fruit and vegetable intake. Consequently, the inverse correlation between plasma β-carotene and lung cancer risk resembles an inverse correlation between vegetable intake and lung cancer risk.

What Do We Know About the Pathological Role of Dietary Components in Lung Carcinogenesis?

Experimental evidence (animal studies, cell culture, etc.) indicates that dietary components (e.g., antioxidants, vitamins, trace elements) intervene at distinct stages of lung carcinogenesis. More work needs to be done to understand the relevance of these observations to human lung carcinogenesis.

Most of the preclinical studies were performed with animal strains selected for enhanced cancer development, and very high doses of carcinogens were used to shorten the time for cancer development. Therefore, although preliminary hints on the preventive activity of dietary components can be obtained from such studies, they must be confirmed by observations on the human population.

From in vitro and in vivo studies there is some evidence that carotenoids (lycopene, lutein, β-carotene, and others), vitamin A, vitamins E and C, and some trace elements interfere with early stages of lung carcinogenesis. In addition, oxidative stress seems to be involved in lung carcinogenesis, especially in smokers. As a consequence, the use of antioxidative vitamins is recommended.
without any knowledge concerning their specific preventive action in lung carcinogenesis.

With respect to antioxidative acting vitamins and trace elements, there are some observational data showing lung cancer preventive effects, especially in smokers. In some prospective studies, an inverse relationship between plasma levels of either vitamin E or vitamin C or selenium and lung cancer incidence was demonstrated. However, in about 50% of all studies dealing with this question, the dietary intake or plasma level of these micronutrients was not related to lung cancer risk.

In basic experiments it was demonstrated that carotenoids like lycopene or β-carotene are involved in the modulation of factors interfering with neoplastic transformation or neoplastic signal transduction. However, it cannot be excluded that, basically, retinoic acid, formed either from provitamin-A carotenoids or by interference of non-provitamin-A carotenoids with intracellular vitamin A metabolism, is the main anticarcinogenic compound, derived from provitamin-A carotenoids.

**How Does Smoking Interfere with Nutrition?**

Smoking is associated with lower food intake (including vegetables and fruit) and higher alcohol consumption. Even in smokers with adequate nutrition, there is evidence that plasma concentrations of some nutrients, including some carotenoids, vitamin C, and folates, are lower than would be expected from their dietary intake.

There is overwhelming evidence from observational studies that a higher than average consumption of fruit and vegetables is protective against many diseases and disorders prevalent in industrialized societies. This protection includes a reduced overall occurrence of human cancers and a reduced risk of lung cancer, particularly among smokers. Unfortunately, it has proved difficult to progress from this generality and to determine what are the specific dietary components, if any, responsible for the observed protection. One problem lies in determining whether health benefits derive directly from the fruit and vegetables or result from a displacement of other components of diet, or whether high fruit and vegetable consumption is simply an index of economic well-being or some other lifestyle factor(s). However, intervention studies at the level of diet tend to confirm observational studies and so support a direct role for fruit and vegetables. The few interventions made with specific compounds naturally found in fruit and vegetables have been less than successful (see below).

**IN VITRO MODELS**

Most attempts to identify the chemoprotective components in diets rich in plant foods have involved monitoring specific metabolic events in the test tube or in cell cultures, with some isolated compounds being further tested in animal cancer models. The limitations of chemically induced cancers with their dependence on large doses of mutagen, in contrast to a lifelong exposure to multiple genotoxic agents, are well recognized. However, this said, induced tumorigenesis in animals is probably a more appropriate model for esophageal and pulmonary cancer in smokers, with their high carcinogen exposure, than for many other cancers.

Several compounds of dietary origin have been shown to inhibit formation of esophageal tumors and lung cancer in rats and mice. Ellagic acid, a phenylpropanoid found in fruit and nuts, and phenethyl isothiocyanate, one of many organosulfur compounds derived from brassicas and *Alium* species, will inhibit nitrosamine-induced esophageal and pulmonary cancers and prevent DNA adduct formation in laboratory animals.
Both of these are examples of compounds that are thought to act very early in carcinogenesis by inhibiting the metabolic conversion of a procarcinogen to a carcinogen. However, it is unlikely that this is the only mechanism of action since, for example, ellagic acid can activate phase II detoxification, complex with some carcinogens, and bind to sites of adduct formation on DNA.

Ellagic acid, a product of phenylpropanoid metabolism in plants, is just one of many hundreds of similar compounds consumed daily as part of a normal diet. As such, ellagic acid shares the general potential of phenylpropanoids to interact with many aspects of mammalian metabolism relevant to cancer initiation and development. Typical of the properties that have been demonstrated in vitro is the ability to:

- Act as an antioxidant
- Enhance antioxidant enzyme activities
- Activate phase II activity
- Modulate P450 activities
- Inhibit the arachidonic acid cascade
- Modify signal transduction
- Inhibit both RNA and DNA synthases
- Competitively bind to a variety of receptors

DNA DAMAGE

Virtually all phenylpropanoids, and many other food-derived compounds with phenolic functionality, will undergo one-electron oxidations, reducing the recipient molecule. The redox potential of most phenylpropanoids at physiological pH will allow the reduction of reactive oxygen species to occur, and thus most compounds of this type have an antioxidant capacity. Although comparative studies have shown that, individually, phenylpropanoids have a far lower antioxidant capacity than the more abundant α-tocopherol or the isoprenoid-derived carotenoids, their collective importance cannot be overlooked.

Protection against cancer initiation must involve reduction of DNA damage, whether caused by alkylation, bulky adduct formation, or oxidation. However, a view of cancer initiation based on a radiation model (i.e., an accumulation of random damage in stem cells) is overly simplistic.

Present knowledge would stress the importance and differential susceptibility to damage of tumor suppressor genes, and in the case of lung cancers, the K-ras oncogene and the hot-spots within these genes. While reduction of oxidative stress, whether exogenous or endogenous in origin, remains important, the substantially higher incidence of K-ras mutations in smokers thought to be caused by benzo[a]pyrene points to the value of dietary agents able to block the metabolic activation of this and other tobacco-related procarcinogens. Transformation of procarcinogens, once absorbed, is generally catalyzed by P450 enzymes, and the ability to specifically inhibit the appropriate isoform of P450 is one commonly suggested mechanism of protection by dietary agents.

INFLAMMATORY AND IMMUNE RESPONSES

As dietary compounds with phenolic functionality will readily donate an electron, many metalloenzymes that depend on redox cycling for their catalytic action are vulnerable to inhibition by dietary compounds. These include the key enzymes involved in eicosanoid metabolism, which probably accounts for the anti-inflammatory properties of dietary compounds such as curcumin, the yellow pigment of turmeric.

Dietary compounds also can boost the immune response, affecting particularly the T-cell population and cytokine production by the T-lymphocytes. Although the mechanism underlying the various responses of the immune system to dietary compounds is poorly understood, it could arise, in part, from the modulation of eicosanoid metabolism.
Reduced inflammation and increased surveillance by the immune system could potentially slow cancer progression, although the extent to which diet can produce this response is unknown.

Laboratory studies have shown that compounds found in fruit and vegetables have the potential to act at all stages of carcinogenesis, from initiation to metastasis, but that they are likely to be most effective in inhibiting carcinogen formation and otherwise reducing DNA damage. Most compounds produce multiple effects when tested in vitro, and any one metabolic effect usually can be produced by several compounds. Effects also may be concentration dependent, protective at low concentration but cytotoxic or genotoxic at higher levels.

For these reasons it may be inappropriate to search for the health-preserving properties of plant foods in a single compound or a few related compounds. Protection may lie in the collective effects of many compounds, which individually occur or are absorbed in small amounts.

What Do the CARET and ATBC Studies Tell Us (Including the Recently Published Data) and What Are the Consequences for Future Studies?

Smokers do not benefit from chemoprevention with β-carotene. On the basis of the above studies it can be reasonably concluded that there might even be additional risks from β-carotene supplementation in current smokers. Baseline levels of β-carotene are inversely associated with lung cancer incidence in both studies, consistent with β-carotene reflecting dietary or lifestyle factors. It also appears that the particular combinations of the β-carotene with either vitamin A or vitamin E do not provide the expected protection against lung cancer.

Possible beneficial effects of balanced diets cannot be tested using pharmacological approaches. In the case of β-carotene, a serum concentration of 0.5 µmol/l represents the optimal physiological concentration associated with the lowest risk in epidemiological studies. This can be achieved by an intake of 4 to 6 mg/day from dietary sources.

It should be noted that epidemiological data indicate that consumption of food that contains β-carotene was associated with decreased risk for lung cancer development. In the context of the CARET and ATBC studies, this may be interpreted as either that the level of β-carotene in the food is sufficient and pharmacological doses are increasing the risk or that other constituents of diet that accompany β-carotene (e.g., α-carotene or lycopene) may provide the protective effects.

CARET and ATBC studies clearly tell us that the extra probation of observational studies to an interventional approach is not the way to prove the more or less justified hypotheses of epidemiological studies. The basis of the nutrient-based cancer prevention hypothesis may need revision. It may be that no single component of the diet is preventive in a physiological case, but rather it is the specific pattern of micronutrients in the diet that is important.

This is confirmed by recent data from ATBC studies, which show that subjects in the lowest quartile of serum β-carotene (< 0.2 µmol) at the start of the study had higher lung cancer rates compared with subjects in the other three quartiles. Increasing β-carotene plasma levels alone has no preventive effect.

What Are the Consequences of These Studies?

These conclusions are not meant to discourage further cancer prevention studies. Future large population studies should be based on hard experimental evidence supported by the use of intermediate biomarkers.

The question arises whether an in-
take of micronutrients more than 10 to 15 fold higher than the usual intake and 2 to 3 fold higher than the highest possible intake by nutrition is a physiological or pharmacological approach. A physiological approach considers physiological activities of vitamins. A pharmacological approach, however, might consider vitamin actions far different from their physiological role. We have to take into consideration the fact that the pharmacological dose should be restricted to an interventional approach and would not be useful for prevention.

Data from observational studies cannot be transferred to an isolated component, e.g., β-carotene, because the intake of this substance is always associated with an intake of the surrounding nutritional matrix. That means that components of this matrix can, either isolated or correlated with their nutritional parameters, exert their antineoplastic effects.

Animal experiments must give clear-cut data that the isolated component prevents lung cancer. However, there is no evidence that isolated β-carotene prevents lung cancer. In contrast, there are data that show a high intake of β-carotene lowers the level of retinol palmi-tate in rat lung tissues. Retinol esters can serve as a source of intracellular precursors of retinoic acid. Retinoic acid is essential for regular growth and differentiation of the respiratory epithelium. Vitamin A deficiency, however, leads to the formation of metaplastic changes that might promote the formation of neoplasias. Furthermore, vitamin A inhibits tumor development in a variety of animal and human studies.

A β-carotene–induced alteration of cellular vitamin A metabolism might be one factor that might explain the increased lung cancer risk in the supplemented group in the ATBC study. Before further intervention studies with isolated micronutrients are carried out we need more data from experimental studies that clearly show the interaction of the isolated component and carcinogenesis.

It is further argued that oxidative modification of cellular components is involved in lung cancer carcinogenesis. β-Carotene and other antioxidative vitamins (C and E) are important compounds that protect lung tissues from oxidative modification. Whether the decrease of vitamin E in plasma following carotene supplementation results in an antioxidative imbalance in the respiratory system remains to be elucidated.

**Special Nutritional Recommendations for the Primary Prevention of Lung Cancer**

To lower the risk of lung cancer and other types of cancer, it is recommended that

- Smokers should stop smoking, because at present there is no dietary regimen that would prevent or lower the frequency of lung cancer in smokers
- Ex-smokers and people who have never smoked should consume a diet that contains five or more portions of vegetables and fruits per day, which would achieve serum levels of micronutrients associated with the lowest risk of lung cancer. Vegetable portions should include a wide variety of uncooked and cooked leaf and root vegetables.

**Are There Special Nutritional Recommendations for the Secondary Prevention of Lung Cancer?**

At present there is no evidence that any type of diet can replace treatments such as surgery, chemotherapy, and radiotherapy. Cancer patients can benefit from appropriate dietary regimens during treatment to reduce side effects or to improve their performance status. The same diet that is recommended for preventing the occurrence of primary tumors is also applicable for preventing the occurrence of second primary tumors. Large prospective studies are ongoing to explore the ef-
ficacy of specific compounds of dietary origin (antioxidants, vitamin A and other retinoids) to prevent this problem.

It is well recognized that multiple primary cancers may arise in various organs simultaneously exposed to the carcinogenic effect of tobacco, as a consequence of the “field cancerization” phenomenon. In particular, second primary lung cancers occur in 10% to 20% of patients cured for a prior lung cancer, and this population is an ideal group in which to test active chemoprevention strategies.

Following the initial favorable experience of small randomized trials showing a protective effect of adjuvant treatment with natural vitamin A or synthetic retinoids against second primary tumors, several large prospective trials are now ongoing to assess the chemopreventive value of retinol palmitate, 13-cis-retinoic acid, and N-acetyl-cysteine (NAC), a potent antioxidant and precursor of natural glutathione. These trials have already enrolled a few thousand patients with prior tobacco-related cancers, and the results are expected within the next 2 to 3 years.

The European Chemoprevention Study (Euroscan) cooperative study was set up in 1988 as a joint venture of the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer and Head and Neck Cancer Cooperative Groups to test the efficacy of two agents with different preventive properties: retinol palmitate and NAC.

Eligible patients were those previously treated for squamous cancer of the larynx (Tis, T1–3, N0–1) squamous cancer of the oral cavity (T1–2, N0–2), or non–small cell lung cancer (pT1–2, N0–1 and T3, N0). Four treatment arms were planned in a $2 \times 2$ factorial design: (a) retinol palmitate and NAC; (b) retinol palmitate; (c) NAC; (d) no treatment, randomization has taken place after surgery and/or completion of radiotherapy.

Retinol palmitate has been administered at the daily oral dose of 300,000 IU for the first 12 months, followed by 150,000 IU for 12 additional months; NAC at the daily dose of 600 mg for 2 years. Minimal follow-up included physical examination every 3 months and a chest radiograph every 6 months. Endpoints of this study are relapse of prior cancer, occurrence of new primary cancers, and survival. The accrual was closed in August 1994, when 2,595 patients had entered the trial. The first analysis is under way and the results will be available by the end of 1997.

Two similar chemoprevention trials were launched in the United States in 1992 by the US Intergroup organization: one on head and neck patients and the other on resected stage I non–small cell lung cancer. Both studies aimed at entering more than 600 patients in each arm to be treated with oral 13-cis-retinoic acid at the dose of 30 mg/day or placebo.

In addition to the main endpoints, secondary prevention trials offer a unique opportunity to identify specific biomarkers of lung carcinogenesis to be used in the future to select the best candidates for specific intervention programs and also monitor the results. In fact, to increase the cost:benefit ratio of intervention plans, specific subpopulations of very high risk individuals should be identified on the basis of constitutive or acquired abnormalities detectable in the target tissues. On the other hand, biological intermediate endpoints will become essential for monitoring the efficacy of preventive strategies in a shorter term, before the actual occurrence of invasive cancer.
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American Cancer Society
Cancer Control Career Development Award for Primary Care Physicians

The American Cancer Society is pleased to announce the 1999 Cancer Control Career Development Award for Primary Care Physicians. This award is intended to develop academic leaders in primary care specialties emphasizing cancer control: family practice, general internal medicine, obstetrics and gynecology, and pediatrics. Through the Cancer Control Career Development Award, the ACS seeks to support individuals in supervised programs that will develop the candidate’s clinical and teaching expertise and his or her capacity to perform independent clinical research or develop innovative curricula in cancer control. It is anticipated that physicians trained under these awards will improve cancer control through involvement in primary care practice, education, and scholarly activities related to cancer control.

Candidates for first-year Cancer Control Career Development Awards for Primary Care Physicians may not have an academic rank above that of Assistant Professor and must not be tenured or be the section head (or equivalent) in their discipline. These awards are intended to support the early development of academic careers that place emphasis on cancer control; physicians with well-established careers and substantial research funding should not apply. In addition, candidates for these awards must be citizens or noncitizen nationals of the United States, or its possessions or territories, or must have been lawfully admitted to the United States for permanent residence at the time of the application.

This is a three-year award. The stipend for the award is $50,000 for the first year, $55,000 for the second year, and $60,000 for the third year. The application deadline is October 1, 1998, for awards to begin July 1, 1999.

To obtain further information or application materials, please contact your local grants administration office. If you are unsure whether your institution received these materials, information is available from: 404-329-7558 or 404-329-5734 (voice), 404-321-4669 (fax), grants@cancer.org (e-mail), or http://www.cancer.org/grants.