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Diet and Human Oral Carcinoma in Europe

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There are substantial variations in incidence and mortality from oral and pharyngeal cancer in Europe, with systematic tendencies towards increasing rates in most European countries, particularly in younger males. Most of the geographical differences are due to tobacco and alcohol consumption, which explain over three quarters of approximately 20 000 deaths from oral cancer registered every year in Europe, excluding the former Soviet Union. Nonetheless, dietary factors have an established and quantifiable role in oral carcinogenesis in Europe. Two studies showed a significant protective effect by vegetables and fresh fruit, which appeared particularly strong and consistent for fruit, but were not explained by measures of intake of beta-carotene or other micro-nutrients. Although it is not clear whether the observed associations simply reflected a generally poorer nutritional status of oral cancer cases, they open interesting perspectives for aetiological research and prevention, since about one in six oral cancers in European populations can be attributed to dietary deficiencies or imbalances.
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INTRODUCTION

THERE IS an approximately 10-fold variation in incidence and mortality from oral and pharyngeal cancer across Europe. Among males, in Calvados, France, the oral cavity was the first-ranked site for incidence, even higher than the lung, while in Greece, Finland or the Netherlands oral cancer was a rare neoplasm, accounting for about 1% of all cancer deaths in males. In females, oral cancer rates were low throughout Europe, and the range of variation was of approximately a factor of two between the highest rates in Hungary, Ireland and Scotland and the lowest ones in Greece, Bulgaria and Spain (Fig. 1) [1].

More important, and more relevant on a public health scale, are recent trends in mortality from oral and pharyngeal cancer [2]. Substantial increases were observed in most European countries, particularly from the mid 1970s onwards, to reach overall age-standardised rates (world standard) of 14.5 in France, 12.5 in Hungary, and over 5/100 000 in several countries, including Czechoslovakia, Switzerland, Italy, Yugoslavia, Germany, Austria, Poland, Spain and Portugal. Upward trends are more pronounced in young and middle age males. Truncated rates, for instance, increased from 4.1 to 13.4/100 000 in Austria, from 3.8 to 6.6 in Belgium, from 13.4 to 32.3 in France, from 2.2 to 14.0 in Germany (former Federal Republic), from 7.0 to 12.2 in Italy, from 3.4 to 11.8 in Poland, from 3.4 to 11.5 in Spain, from 3.8 to 12.5 in Yugoslavia. Only in Scandinavia was mortality from oral cancer approximately stable (in Norway and Sweden) or downwards (in Finland) [2].

Inspection of age-specific rates shows substantial increases in younger ages in most European countries (see Fig. 2 for trends in young adults, i.e. between 20 and 44 years in selected countries). This indicates that, in the absence of adequate intervention, the epidemic of oral and pharyngeal cancers is likely to further spread among European males during the next few decades [2].

Alcohol and tobacco have long been recognised as the main risk factors for oral and pharyngeal cancer in Europe and largely explain the substantial excess rates in France, as well as the high rates of several central European countries—although the proportions of attributable risk to alcohol and tobacco vary considerably from area to area [3–5]. There are, however, also several epidemiological indicators that nutritional factors, and specifically dietary deficiencies, are associated with oral and pharyngeal cancer risk. They will be reviewed in the present article, with specific attention to European data.

DIET AND HUMAN ORAL CARCINOMA

Iron deficiency and primary sideropenic anaemia, since their first descriptions early this century, have been associated with malignancy of the oral cavity and other upper digestive sites [5–7]. This syndrome (Plummer–Vinson or Paterson–Brown–Kelly) was particularly common in Scandinavia and other Northern European countries, but the risk of these cancers was not associated with iron deficiency in tropical countries, and similar lesions were not produced by an iron-deficient diet in animals. [8–11]. Thus, other nutritional deficiencies are likely to be implicated, including those of niacin, riboflavin, thiamine and pyridoxine. Diffuse lesions of the upper alimentary tract were also observed in pellagra, a life-threatening disease endemic in the Midwestern and Southern United States as well as in Central Europe and Northern Italy up to the beginning of this century. Pellagra was due to a complex deficiency of niacin and other micro-nutrients, and entails widespread inflammation of the mucous surfaces of the oral cavity, pharynx and oesophagus with consequent dysphagia [12, 13].

Over the past three decades, several analytical epidemiological studies have been published on dietary correlates of oral

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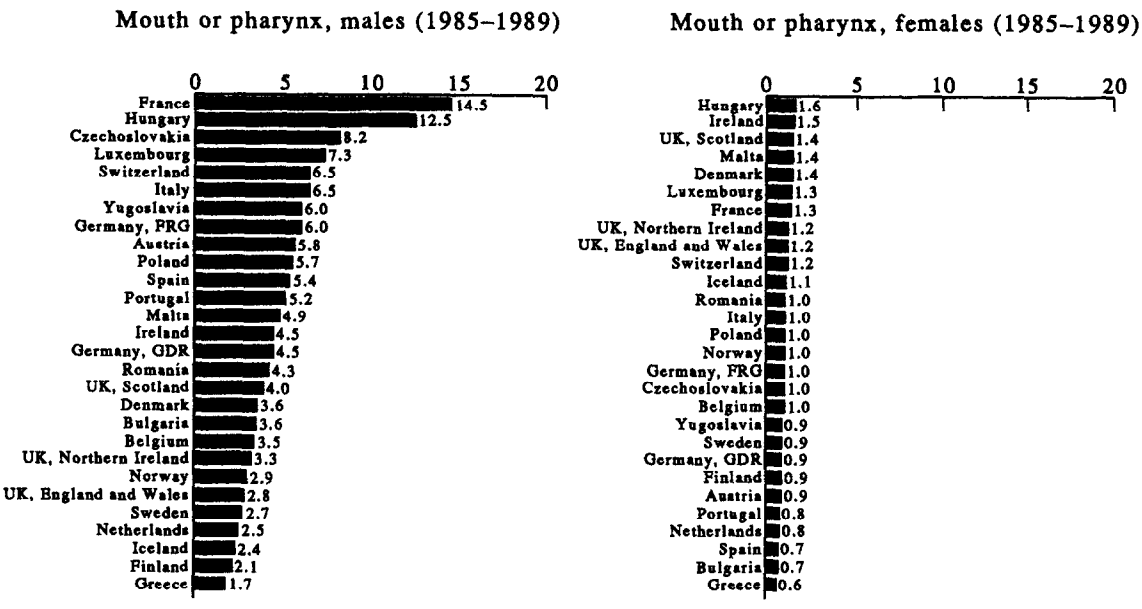

Fig. 1. Geographical variations of oral and pharyngeal cancer in Europe. Age-standardised death rates (world standard), 1985–1989.

cancer. Earlier work found little association with any specific food, dietary item, or method of preparation [14], but subsequent studies showed decreased risks with increasing consumption of vitamins A and C, fresh fruit, green leaf vegetables and other vegetables [15–17]. More recent work from Brazil [18], as well as the largest study available to date on diet, oral and pharyngeal cancer (a population-based case-control investigation conducted in four areas of the United States [19]), seemed to indicate a specific protection by fresh fruit and specifically citrus fruit intake, which was not explained by beta-carotene, vitamin C or fibre content of fruit and vegetables.

There is some indication, from chemoprevention trials, that both vitamin A and its precursor beta-carotene appear to have some activity in reducing indicators of dysplastic lesions in the oral mucosa (micronucleated exfoliated cells and leukoplakia). This evidence is, however, too preliminary to find clinical application outside controlled trials [20].

DIET AND ORAL CANCER IN ITALY

Two studies have been published on diet, nutrition and cancers of the oral cavity and pharynx in Europe. The largest one [21] was based on 302 cases and 699 controls from a high risk area (Pordenone province, north-east Italy). The high risk is essentially due to the long-lasting habits of tobacco use in this area, and to the very high levels of alcohol consumption, since over 50% of cancer cases reported consumption of eight alcoholic beverages per day or more.

Besides strong associations with tobacco, alcohol and lower social class, and after allowance for these factors in multivariate analyses, this study found positive associations with more frequent consumption of pasta or rice, polenta, cheese, eggs and pulses, with relative risks (RR) of the order of 1.4–1.9 for the highest versus the lowest intake tertile (Table 1). Further, there was a direct association with higher frequency of daily meals (RR = 1.7 for ≥ 4 vs. ≤ 2 meals), which were essentially interpreted as indicators of a poorer and badly balanced diet, thus probably reflecting unfavourable socio-economic conditions. In contrast, more frequent consumption of selected fruits and vegetables, and particularly of carrots, fresh tomatoes and green vegetables, was associated with reduced risk of oral and pharyngal cancer, with RRs of the order of 0.5–0.7 for the highest versus the lowest tertile (Table 1).

A separate analysis of the same dataset was focused at investigating the role of maize on the risk of oral and pharyngeal, as well as of oesophageal cancer [13]. Strong direct associations were observed with all upper digestive sites. The relative risks were of the order of 2–3 for the highest versus lowest frequency of consumption (Table 2). Maize is easier to grow and more resistant to fungus and attacks by birds than other grain. However, particularly if refined, maize is less nutritious than other grains, and can cause deficiencies of several micronutrients (chiefly riboflavin and niacin).

Riboflavin deficiency has been suggested as one of the deficiencies that cause the Plummer–Vinson syndrome, a long-recognised precancerous lesion of the upper digestive tract. Maize is not only low in niacin and its precursor tryptophan, but also contains large quantities of leucine, which is capable of interfering with oxidation-reduction reactions. Like the Plummer–Vinson syndrome, pellagra, a common and important disease in that area until the beginning of the current century, can result in widespread inflammation of the mucous surface, dysphagia and oral and oesophageal lesions.

Alcohol may aggravate the nutritional deficiencies introduced by a maize-rich diet. Alternatively, mucous lesions caused by niacin and/or riboflavin deficiency may enhance the topical reaction of alcohol, possibly enhancing the absorption of carcinogenic compounds.

The second European study of diet and oral cancer was a case-control investigation of 105 cases and 1169 controls from Greater Milan, an intermediate risk area from Northern Italy [22]. Besides significant and direct associations with tobacco (RR = 11.0 for current vs. never smokers) and alcohol (RR = 5.8 for the upper vs. the lower consumption level), frequencies of consumption of six food items—milk (RR = 0.4 for the upper vs. the lower intake level), meat (RR = 0.4), cheese (RR = 0.7), carrots (RR = 0.4), green vegetables (RR = 0.6), and fresh fruit (RR = 0.2)—were inversely and significantly

related to oral cancer risk (Table 3). The strongest protection was apparently related to frequent fruit consumption, and this was independent from major potential confounding factors, including tobacco, alcohol and social class indicators.

The questionnaire sought specific information on consumption of a number of important sources of vitamin A in the Italian diet and, although based on a restricted selection of indicator foods, was sufficient to study this micro-nutrient. As in American data [19], beta-carotene but not retinol was inversely related with risk of cancer of the oral cavity and pharynx, but the association was weaker than that with measures of fruit consumption [RR for the upper level = 0.3, 95% confidence interval (CI) 0.2–0.4, Table 4 based on an updated series of 166 cases and 1355 controls]. It is likely, therefore,

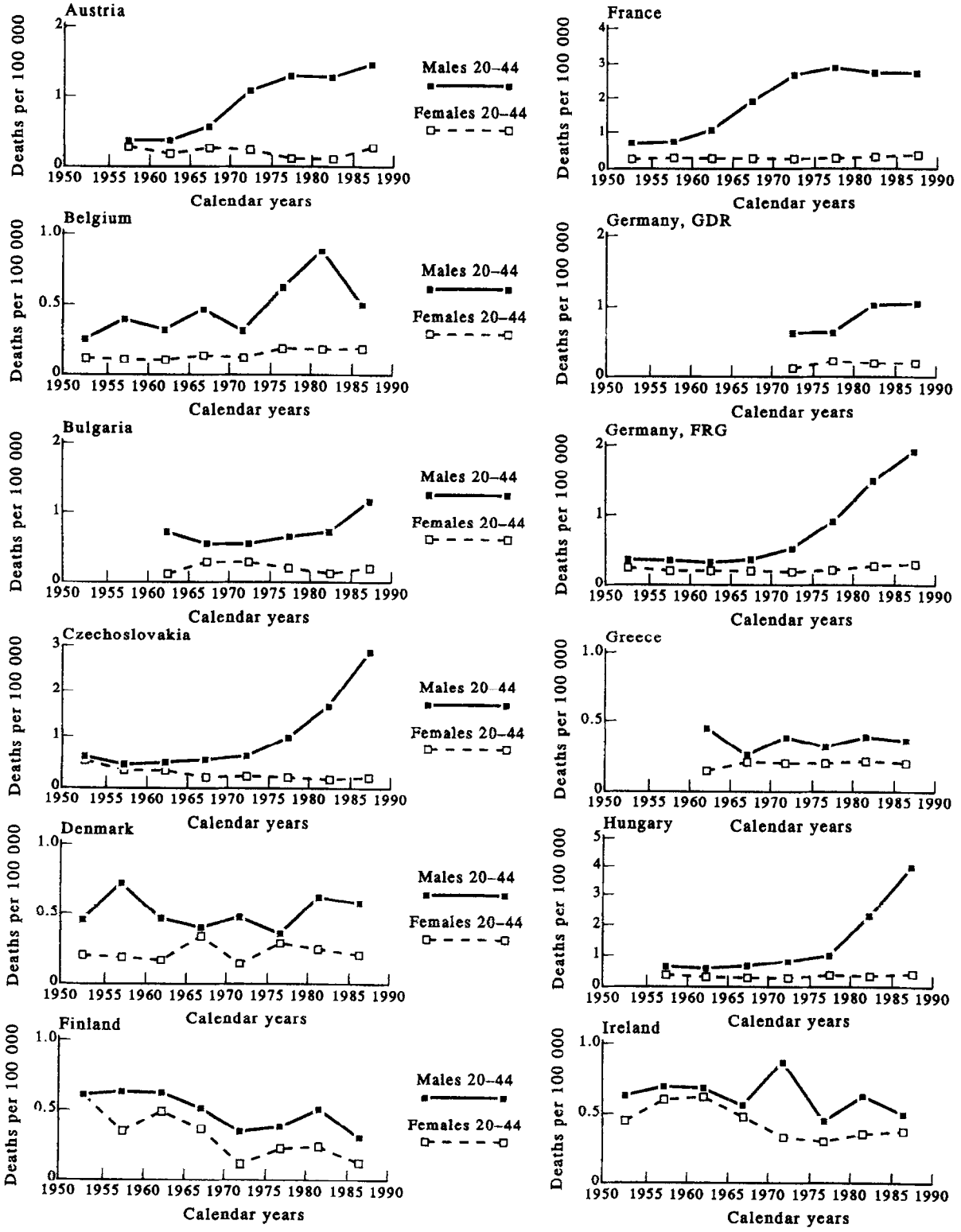

Fig. 2. Trends in age-standardised death certification rates from oral and pharyngeal cancers in young adults (20–44 years) in main European countries.

that the inverse relationship with beta-carotene was not specific, but simply reflected a generally poorer nutritional status in the cases. Still, the consistent observation that fruit consumption appears to be a particularly important protective factor against oral and pharyngeal cancer is of potential interest, in terms of aetiological clues and preventive implications.

CONCLUSIONS

In the late 1980s, about 20 000 deaths from oral and pharyngeal cancer were registered every year in Europe, excluding the former Soviet Union [2]. Of these, over three quarters are attributable to combined exposure to tobacco and alcohol abuse, although the relative importance of these two main risk factors may vary from population to population.

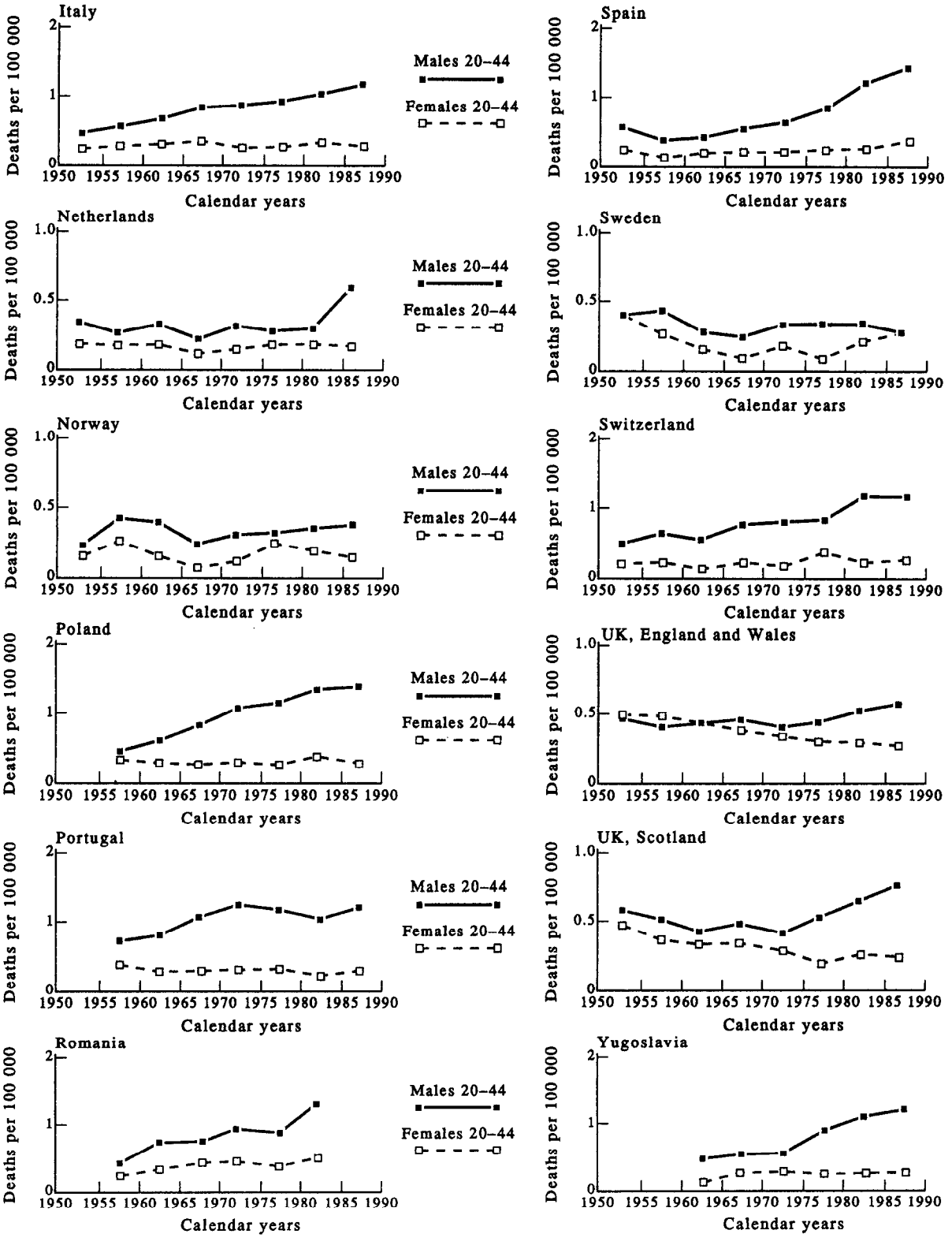

Fig. 2. Continued.

These two main factors notwithstanding, dietary factors have nonetheless a well established and quantifiable role on oral and pharyngeal cancer risk in Europe. The precise dietary pattern which may entail a reduced oral cancer risk, or the specific micro-nutrients which may exert some protection are still not completely defined, but it is clear that a diet poor in fresh vegetables, and, particularly, fresh fruit is associated with elevated oral and pharyngeal cancer risk. Also where affluency allows a diet relatively better balanced than in the poorest areas of the world where oral cancer shows its peaks [23], higher than the average intake of vegetables and, particularly, fresh fruit, can reduce by 2–3-fold the risk of this neoplasm. Various indices of micro-nutrients, including vitamin C and beta-carotene are also inversely correlated with oral cancer risk, but generally less strongly than broad food groups. Therefore, the time for a translation of the clear benefit of fresh fruit and vegetables into more specific micro-nutrient supplementation seems still to come for oral and pharyngeal cancer as well as for other common neoplasms.

Although intake of proteins and of various protein-rich foods is often inversely associated with cancer risk [22], total intakes of calories and fat, butter, eggs and starchy foods emerged in some investigations as significant risk factors [13, 21]. The possible adverse effect of these food items, often quoted as risk factors for other neoplasms such as cancer of the breast and colon–rectum, is generally overlooked in respect to neoplasms of the upper digestive tract, but, perhaps, not rightly so. It is conceivable that the elevated risk associated with frequent consumption of fats and some starchy foods (e.g., maize) is another indicator of less affluent diet, potentially poor in micronutrients which can prevent carcinogenesis in the upper digestive tract. In most of the groups where cancer of the oral cavity has been studied, intake of large amount of alcohol, of the order of 1 000 kilo-calories or more per day is reported by the majority of cases [21]. Alcoholic beverages provide none of the daily requirements for micro-nutrients and protein and, therefore, can be considered empty calories. The impact of such empty calories can be aggravated by a monotonous diet which can obviously be based in different locations on very different staple foods (e.g. bacon and sausages in American Blacks, potatoes in northern France, maize in mountainous areas of northern Italy). Lack of variety in the major sources of caloric intake can, therefore, contribute with alcoholic beverages to lower the habitual intake of known or still unknown protective micro-nutrients.

In conclusion, whereas measures against smoking and heavy alcohol drinking remain of high priority, approximatively 15% of oral cancers can be attributed to dietary deficiencies (or unbalances) [22], which may correspond to 3 000 deaths per year in Europe avoidable through the application of the currently available (however crude) knowledge of dietary correlates of oral carcinomas.

Table 1. Multivariate relative risks of oral and pharyngeal cancer in relation to selected food items. Pordenone, Italy, 1984–1989 (302 cases, 699 controls)

	Relative risks* for frequency of consumption		
Food item	1 (Low)†	2 (Intermediate)	3 (High)
Pasta or rice	1	1.1	1.4
Polenta	1	1.2	1.8
Cheese	1	1.0	1.7
Eggs	1	1.4	1.6
Pulses	1	1.4	1.9
Carrots	1	0.8	0.7
Fresh tomatoes	1	0.7	0.5
Green peppers	1	0.6	0.5

*Derived from a model including terms for age, sex, occupation, smoking and drinking habits, and all the food items listed.
†Reference category (from Franceschi *et al.*, 1991 [21]).

Table 2. Relative risks for cancers of the oral cavity, pharynx and oesophagus associated with frequency of maize consumption: Pordenone, Italy, 1985–1989

	Relative risks for frequency of consumption of maize (servings/week)*		
Cancer site	Never-occasionally†	1–2	≥3
Oral cavity	1	1.5	2.5
Pharynx	1	1.5	2.5
Oesophagus	1	1.2	2.1
All sites	1	1.4	2.3

*Derived from multiple logistic regression equations, including terms for age, education, occupation, tobacco use, and frequency of consumption of fresh fruits, vegetables, and maize. P values: <0.01 for all trends.
†Reference category (from Franceschi *et al.*, 1990 [13]).

Table 3. Multivariate relative risks of oral and pharyngeal cancer in relation to selected indicator foods. Milan, Italy, 1987–1989

	Relative risks (and 95% confidence intervals) for frequency of consumption*		
Food item	1 (Low)†	2 (Intermediate)	3 (High)
Milk	1	1.0	0.4
Meat	1	1.1	0.5
Cheese	1	1.2	0.7
Carrots	1	0.6	0.4
Green vegetables	1	0.9	0.6
Fresh fruit	1	0.6	0.2

*Derived from multiple logistic regression models including terms for sex, age, area of residence, education, social class, and smoking.
†Reference category (from La Vecchia *et al.*, 1991 [22]).

Table 4. Relationship between measures of beta-carotene intake and oral and pharyngeal cancer risk. Milan, Italy, 1984–1991

	Oral cancer	Controls	Relative risk (95% CI)*
Beta-carotene (× 1000 IU)			
<105	91	411	1†
105–150	42	400	0.4 (0.3–0.5)
>150	33	544	0.3 (0.2–0.4)

*Adjusted for age and sex.
†Reference category.

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