



## Review

Dietary factors and oral and pharyngeal cancer risk<sup>☆</sup>Ersilia Lucenteforte<sup>a</sup>, Werner Garavello<sup>a,b</sup>, Cristina Bosetti<sup>a</sup>, Carlo La Vecchia<sup>a,c,\*</sup><sup>a</sup> Dipartimento di Epidemiologia, Istituto di Ricerche Farmacologiche "Mario Negri", via Giuseppe La Masa 19, 20156 Milan, Italy<sup>b</sup> Clinica Otorinolaringoiatrica, DNTB, Università Milano-Bicocca, via Donizetti 106, 20052 Monza, Italy<sup>c</sup> Istituto di Statistica Medica e Biometria, "G.A. Maccacaro", Università degli Studi di Milano, via Venezian 1, 20133 Milano, Italy

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## SUMMARY

We reviewed data from six cohort studies and approximately 40 case-control studies on the relation between selected aspects of diet and the risk of oral and pharyngeal cancer. Fruit and vegetables were inversely related to the risk: the pooled relative risk (RR) for high vegetable consumption was 0.65 from three cohort studies on upper aerodigestive tract cancers and 0.52 from 18 case-control studies of oral and pharyngeal cancer; corresponding RRs for high fruit consumption were 0.78 and 0.55.  $\beta$ -carotene, vitamin C and selected flavonoids have been inversely related to the risk, but it is difficult to disentangle their potential effect from that of fruit and vegetables. Whole grain, but not refined grain, intake was also favorably related to oral cancer risk. The results were not consistent with reference to other foods beverages, and nutrients, but it is now possible to exclude a strong relation between these foods and oral and pharyngeal cancer risk. In western countries, selected aspects of diet may account for 20–25% of oral and pharyngeal cancer, and the population attributable risk increases to 85–95% when tobacco and alcohol consumption are also considered.

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## Introduction

Besides tobacco and alcohol, other risk factors have been studied in relation to oral and pharyngeal cancer, though their role is smaller and less well recognized than that of tobacco or alcohol in most populations.<sup>1</sup> Among these factors, diet and nutrition have been suggested to play an important role.<sup>2,3</sup>

The association between dietary habits and the risk of oral and pharyngeal cancer has been investigated in several studies, both in relation to single food items or groups and to nutrients, micronutrients and food components.

The epidemiological evidence on dietary factors and the risk of cancer of the oral cavity and pharynx has been reviewed. An overall quantitative estimate of the risk of oral and pharyngeal cancer in relation to fruit and vegetable consumption was also provided.

## Materials and methods

Epidemiological studies included in this review were original cohort and case-control investigations published up to June 2008.

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\* Corresponding author. Address: Dipartimento di Epidemiologia, Istituto di Ricerche Farmacologiche "Mario Negri", via Giuseppe La Masa 19, 20156 Milan, Italy. Tel.: +39 0239014527; fax: +39 0233200231.

E-mail address: [lavecchia@marionegri.it](mailto:lavecchia@marionegri.it) (C. La Vecchia).

They were identified through searches of the MEDLINE database, using the keywords: "diet", "food", "fruit", "vegetables", "cereals", "meat", fish, "eggs", "milk", "cheese", "dairy products", "coffee", "tea", "nutrients", "vitamins", "flavonoids", "neoplasms", "risk factors", "case-control studies", and "cohort studies". Papers were also searched among those quoted as references in the retrieved studies, as well as in a few previous reviews. Only papers in English were considered.

For fruit and vegetables, quantitative overall estimates of the relative risk (RR) of oral and pharyngeal cancer were provided. After assessing the statistical heterogeneity among studies using the  $\chi^2$  test, we pooled the study specific estimates using the "fixed effect" model,<sup>4</sup> or the "random effect" model when a significant heterogeneity was found.<sup>5</sup> Whenever available, RR estimates adjusted for multiple confounding factors were used; We did not include in the pooled estimates the results from a few studies based on limited numbers of subjects (less than 120 cases), including data for total vegetables or total fruit, or not providing the 95% confidence interval (CI).

## Food groups

## Fruit and vegetables

At least three cohort studies investigated the role of fruit and vegetables on the risk of cancer of the oral cavity and pharynx,<sup>6–8</sup> while other three studies evaluated the association for all cancers

of the upper aerodigestive tract (UDT) combined.<sup>9–11</sup> About 40 case-control studies examined the relation with oral and pharyngeal cancer risk.<sup>12–47</sup>

A cohort study of 265,118 Japanese adults found a decreased risk of cancer of oral cavity and pharynx for high consumption of green and yellow vegetables.<sup>6</sup> In the Iowa Women's Health Study (IWHS) on 34,651 postmenopausal women from the USA, and including 53 women who developed oral and pharyngeal cancer, a RR of 0.69 was reported for the highest intake of yellow/orange vegetables.<sup>7</sup> Another US prospective study on 490,802 participants in the National Institutes of Health–American Association of Retired Persons (NIH–AARP) Diet and Health cohort, including 319 cancers of the oral cavity and 142 cancers of the oro-hypopharynx, reported a significant inverse association between total fruit and vegetable intake and cancer of the oral cavity (RR = 0.61), but no association for that of the oro-hypopharynx (RR = 0.90).<sup>8</sup> Moreover, when fruit and vegetables were analyzed separately, a stronger inverse association was found for vegetables, both for cancer of the oral cavity (RR = 0.56 and RR = 0.84, respectively) and for that of the oro-hypopharynx (RR = 0.56 and RR = 1.19, respectively).

Among cohort studies which analyzed the risk of all UDT cancers combined (Fig. 1), a cohort study of 7995 Japanese–American men including 92 incident cancers, reported a RR of 0.65 for frequent consumption of fruit.<sup>9</sup> In a prospective study on 10,960 Norwegian men including 71 UDT cancers, a significant inverse trend in risk was found for oranges, with a RR of 0.5 for the highest level of consumption.<sup>10</sup> Apples, bananas and preserved fruit gave non-significant inverse RRs. However, a total sum–score of fruit showed no significant relation. Likewise, none of the vegetables showed any consistent relation with risk. The European Prospective Investigation into Cancer and Nutrition (EPIC) conducted in ten European countries on 345,904 subjects, and including 352 cancers of the UDT reported a significant inverse relation with total fruit

and vegetables combined (RR = 0.60), and with total fruit (RR = 0.60), while a non-significant inverse association was found for total vegetables (RR = 0.80).<sup>11</sup>

About 30 case-control studies reported inverse associations with oral and pharyngeal cancer for at least one category of vegetables and/or fruit, with reductions in risks of 50–70%.<sup>12–20,22–28,30–33,35,37–43,45–47</sup> Furthermore, most studies that examined the relation with total vegetables reported inverse associations.<sup>13,14,17,18,20,23,24,26,29,32,39–41,45–47</sup> Similarly, most case-control studies which investigated the association with total fruit reported an inverse relation.<sup>12,14,15,17–21,23,24,26,27,29,32,33,36,38–42,45–47</sup> (Figs. 2,3).

The evidence of a beneficial effect of fruit and vegetables on oral and pharyngeal cancer risk has been consistently observed for raw and green/leafy vegetables,<sup>12,15–19,21,22,25,27,28,30,33,37,38,40–42,45,47</sup> tomatoes,<sup>18,25,32,37,39–41,47,48</sup> and citrus fruit.<sup>15–18,22,25,28,30,32,33,35,37,39–42,44,45</sup> Several case-control studies also found consistent inverse associations with carrots,<sup>16,18,19,21,25,33,37,40,41,47</sup> while for other specific vegetables or fruit (such as cruciferous vegetables or apples/pears) the evidence is more limited.

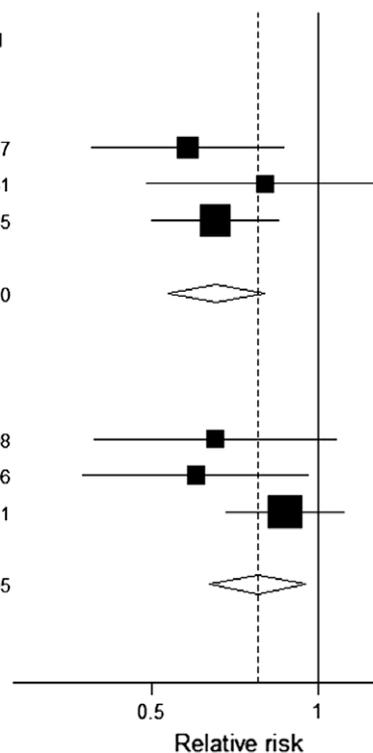
The pooled RR for high vegetable consumption was 0.65 (95% CI 0.53–0.80) from three cohort studies on UDT cancer, and 0.52 (95% CI 0.45–0.61) from 18 case-control studies of oral and pharyngeal cancer; corresponding figures for fruit consumption were 0.78 (95% CI 0.64–0.95), and 0.55 (95% CI 0.47–0.65) (Figs. 1–3).

#### Cereals

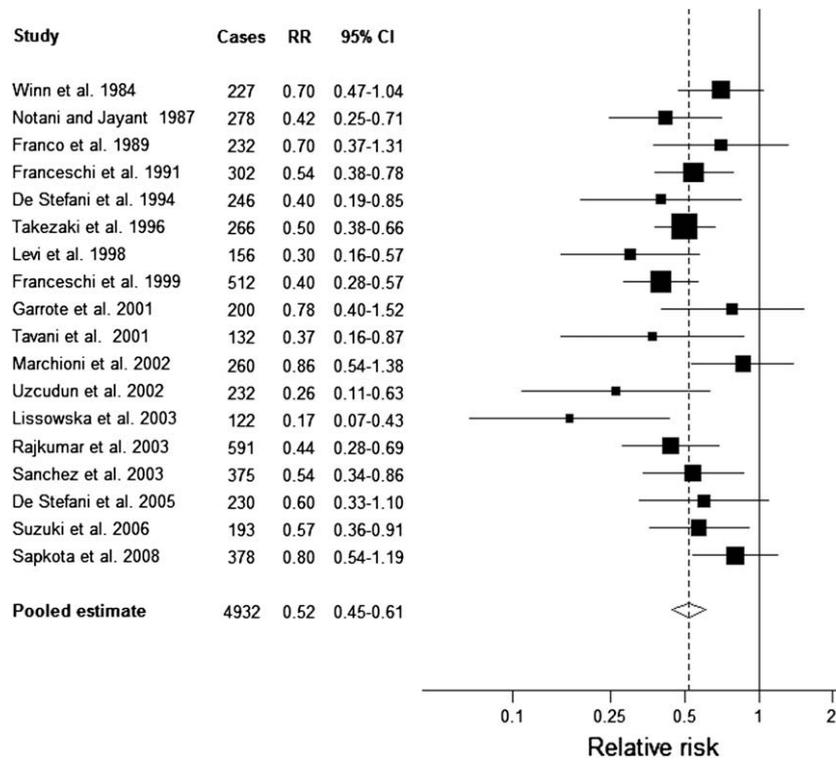
The role of cereals on the risk of cancer of the oral cavity and pharynx was investigated in at least three cohort<sup>7,9,10</sup> and 25 case-control studies.<sup>12,13,15,17–19,21,24,25,28–30,32,34,36,38–41,44,45,49–51</sup>

In the IWHS cohort a significant inverse association was observed for the highest level of intake of whole (RR = 0.47) and refined grains (RR = 0.70).<sup>7</sup> In another cohort study on Hawaii Japanese, consumption of rice was directly associated with the risk

Study	Cases	RR	95% CI
<b>Vegetables</b>			
Kasum et al. 2002	169	0.58	0.39–0.87
Boeing et al. 2006	352	0.80	0.49–1.31
Freedman et al. 2008	787	0.65	0.50–0.85
<b>Pooled estimate</b>	<b>1308</b>	<b>0.65</b>	<b>0.53–0.80</b>
<b>Fruit</b>			
Chyou et al. 1995	92	0.65	0.39–1.08
Boeing et al. 2006	352	0.60	0.38–0.96
Freedman et al. 2008	787	0.87	0.68–1.11
<b>Pooled estimate</b>	<b>1231</b>	<b>0.78</b>	<b>0.64–0.95</b>



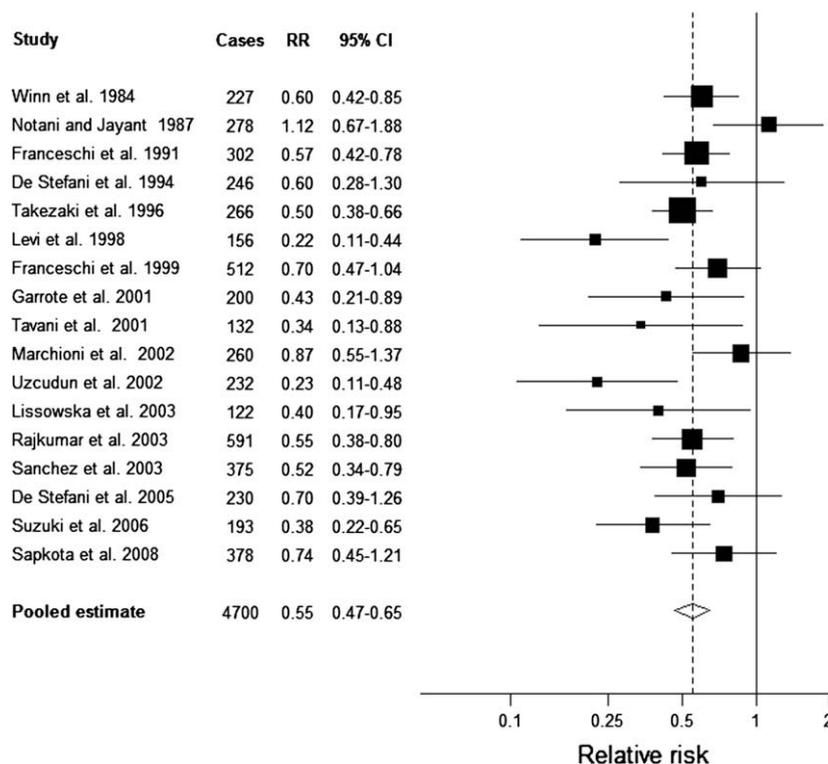
**Figure 1** Relative risks (RR) of upper aerodigestive tract cancers and corresponding 95% confidence intervals (CI) for the highest level of vegetable and fruit consumption from cohort studies.



**Figure 2** Relative risks (RR) of oral and pharyngeal cancer and corresponding 95% confidence intervals (CI) for the highest level of vegetable consumption from case-control studies.

of UDT cancers (RR = 1.43), while consumption of bread was inversely associated (RR = 0.80), although the dose-response relation was not significant.<sup>9</sup> In a prospective study from Norway,

consumption of bread was significantly associated with a reduced risk of UDT cancers, with a RR of 0.2 for the highest level of intake.<sup>10</sup>



**Figure 3** Relative risks (RR) of oral and pharyngeal cancer and corresponding 95% confidence intervals (CI) for the highest level of fruit consumption from case-control studies.

Among case-control studies, some reported an increased risk of oral and pharyngeal cancer with high consumption of cereals and cereal products,<sup>17,18,28,29,32,44,45,49,50</sup> while others reported inverse<sup>12,13,24,30,34,36,38</sup> or no association.<sup>15,25,39–41</sup> This may well reflect different consumption of cereal foods or different correlates of diets rich in cereals in various populations. An inverse association with whole grains bread, wheat bread and pasta was found in various case-control studies,<sup>12,18,19,21,52</sup> although one study found a direct non-significant association with wheatgerm.<sup>51</sup>

#### Meat, fish and eggs

At least two cohort<sup>9,10</sup> and 30 case-control studies<sup>12,13,15–22,25–30,32,34,36–41,44,45,47,51</sup> evaluated meat consumption in relation to the risk of cancer of the oral cavity and pharynx.

A cohort study on Hawaii Japanese found a non-significant inverse relation with total meat, with a RR of 0.77,<sup>9</sup> while another one from Norway reported an increased risk of UDT cancers for high consumption of various types of meat, and no significant relation with a score of total meat consumption.<sup>10</sup>

An increased risk of oral and pharyngeal cancer in relation to meat and meat products was also observed in various case-control studies,<sup>12,15–18,20,22,26,28,30,32,36–38,40,44,45,47</sup> although inverse or no was reported in other studies.<sup>13,19,21,25,27,29,34,39,41,51</sup>

A cohort study of UDT cancers found a non-significant direct association with consumption of fish (RR = 1.37).<sup>9</sup> In another cohort study, a non-significant inverse relation with UDT cancers was observed for fresh/frozen fish, but not for a score of total fish consumption.<sup>10</sup> Conversely, several case-control studies reported a decreased risk of cancer of the oral cavity and pharynx for high consumption of fish.<sup>13,15,17,19,25,28,30,33,38–40</sup> A few other case-control studies, however, found a direct<sup>12,22,32,47</sup> or no association.<sup>18,21,27,36,41,51</sup>

The relation between eggs and oral and pharyngeal cancer risk was evaluated in various studies, providing, however, conflicting results. A direct association was found in a cohort study (RR = 1.33),<sup>9</sup> but no association was observed in another one.<sup>10</sup> Moreover, at least 10 case-control studies<sup>13,18,19,27–30,32,44,45</sup> found a direct association, while a few other studies reported an inverse association<sup>25,39,40</sup> or no association.<sup>12,21,41</sup>

#### Milk and dairy products

At least one cohort study<sup>9</sup> and 25 case-control studies<sup>12,13,15,17–19,21,24–28,30,32,34,36,38–41,44,45,47</sup> investigated the association between consumption of milk and dairy products and oral and pharyngeal cancer risk.

Results on milk have been mixed, with one cohort<sup>9</sup> and eight case-control studies<sup>19,24,25,28,32,39,41,44</sup> reporting inverse associations, and other studies reporting no meaningful<sup>13,18,21,26,30,40,47</sup> or a direct association.<sup>27</sup>

A direct relation with cheese consumption was observed in a few studies,<sup>18,28,30,32,44</sup> although other studies observed an inverse association,<sup>19,39–41,47</sup> and another one found no association.<sup>21</sup>

The relation between yoghurt consumption was considered in a few studies,<sup>32,39–41,47</sup> two of which reported significant inverse associations,<sup>39,41</sup> while the others reported a direct non-significant one,<sup>32,40</sup> and another reported no association.<sup>47</sup>

A few studies observed a direct association with dairy products in general,<sup>15,17</sup> while a few others found inverse<sup>29,36,38,47</sup> or no association.<sup>12,34,45</sup>

#### Coffee, tea and maté

In a cohort study on Hawaii Japanese coffee was directly associated to UDT cancers, while black tea was inversely related and

green tea was not associated to the risk.<sup>9</sup> A prospective study from Norway reported inconsistent inverse associations between coffee consumption and oral and pharyngeal cancer risk.<sup>53</sup> A few case-control studies suggested a protective effect of tea,<sup>21,27,30,44</sup> as well as coffee<sup>19,21,30</sup> on oral carcinogenesis, while other case-control studies found a direct association.<sup>16,18,25,27,54</sup>

Maté – a herbal infusion traditionally consumed in Argentina and some areas of Brazil – was positively related to the risk of oral and pharyngeal cancer.<sup>14,16,20,29,35,44,54</sup> This was attributed to the fact that maté is consumed very hot through a straw, and can thus produce heat damage in the oral cavity.

### Nutrients and other food components

#### Macronutrients

A reduced risk for total fat was reported in a case-control study from China (RR = 0.56),<sup>25</sup> and in a cohort study from the Hawaii (RR = 0.61),<sup>9</sup> while a direct association was reported in two case-control studies from the USA,<sup>15,55</sup> and no association was found in two case-control studies from Uruguay<sup>56</sup> and Greece.<sup>36</sup>

With reference to specific fatty acids, a study from the USA showed a direct association with saturated fat (RR = 1.6 for men and 1.5 for women).<sup>15</sup> Similarly, in an Italian case-control study, a RR of 1.4 was reported for high intake of saturated fatty acids, while the RR was 0.8 for high intake of monounsaturated fatty acids deriving mainly from olive oil and no association was found with polyunsaturated fatty acids.<sup>57</sup> In contrast, in a case-control study conducted in Uruguay an inverse association was observed for saturated fat and a direct one for polyunsaturated fat, while monounsaturated fat was not related to the risk of oral and pharyngeal cancer.<sup>56</sup>

With reference to seasoning fats, a significant association with butter intake was found in all Italian case-control study,<sup>18,30</sup> but not in another one,<sup>19</sup> while an inverse non-significant association was observed in a case-control study from Brazil.<sup>44</sup> Conversely, high intake of olive oil was associated with significantly lower risk, while mixed seed oils and margarine were not significantly related to risk<sup>30</sup> (Table 1).

#### Micronutrients

The IWHS cohort on 34,691 women, and including 33 post-menopausal women with cancers of the mouth, pharynx and esophagus, found inverse associations for consumption of carotene (RR = 0.7) and vitamin C (RR = 0.7), while reported no associations for vitamin E and retinol.<sup>58</sup> Another cohort study of cancers of the UDT Hawaii Japanese found an inverse non-significant association for calcium (RR = 0.67), and a direct one for sodium (RR = 1.26).<sup>9</sup>

Eight case-control studies reported an inverse association with carotene (mainly  $\beta$ -carotene) intake,<sup>15,17,23–25,35,46,59</sup> although another case-control study found a direct non-significant association,<sup>22</sup> and others found no consistent associations.<sup>36,56,60</sup>

**Table 1**

Odds ratios (OR) and corresponding 95% confidence intervals (CI) of oral and pharyngeal cancer according to intake quintile of olive oil and other added fats<sup>30,85</sup>

	Quintile of intake, OR (95% CI)		
	1 <sup>a</sup>	3	5
Olive oil	1	0.7 (0.5–1.1)	0.4 (0.3–0.7)
Mixed seed oils	1	1.0 (0.7–1.4)	1.1 (0.7–1.7)
Butter	1	1.3 (0.8–1.9)	2.3 (1.6–3.5)

<sup>a</sup> Reference category.

**Table 2**Multivariate odds ratios (OR) and 95% confidence intervals (CI) of oral and pharyngeal cancer according to intake of selected flavonoids. Italy, 1991–2007<sup>67,84</sup>

	Quintile of intake					$\chi^2_{\text{trend}}$ (p-value)
	1 <sup>a</sup>	2	3	4	5	
Flavanones						
OR (95% CI)	1	0.90 (0.68–1.18)	0.70 (0.52–0.94)	0.61 (0.45–0.83)	0.51 (0.37–0.71)	22.03 (< 0.001)
Flavonols						
OR (95% CI)	1	0.92 (0.66–1.28)	0.80 (0.57–1.12)	0.65 (0.46–0.92)	0.62 (0.43–0.89)	9.33 (0.002)
Total flavonoids						
OR (95% CI)	1	0.77 (0.56–1.06)	0.64 (0.46–0.89)	0.63 (0.45–0.87)	0.56 (0.40–0.78)	11.92 (0.001)

<sup>a</sup> Reference category.

Inverse associations were also reported for vitamin C,<sup>15,17,23–25,36,46,56,59–62</sup> although two studies found no association.<sup>22,63</sup>

Case-control studies regarding other vitamins, such as vitamin E,<sup>46,59,62,63</sup> vitamin A,<sup>25,61,62</sup> and folate<sup>15,64</sup> suggested a beneficial effect on oral and pharyngeal cancer of these nutrients, too. Moreover, a beneficial effect was suggested also for iron,<sup>25,36,51,59,62</sup> and calcium.<sup>25,36,51,59</sup> Severe iron deficiency in Plummer–Vinson (Patterson–Kelly) syndrome in the early 20th century in Sweden had been associated to excess oral cancer risk.<sup>65</sup> Iron deficiency produces free radicals and reactive oxygen species which cause cell injury.<sup>66</sup>

A few other studies investigated the relation with riboflavin,<sup>15,25,29,36,55,59</sup> retinol,<sup>15,17,24,36,55,59–61</sup> and thiamine,<sup>15,25,29,36,55,59,62,63</sup> but did not report any consistent relation with the risk.

### Flavonoids

Flavonoids – a class of polyphenols from vegetable origin, with antioxidant, antimutagenic and antiproliferative properties – were investigated in two case-control studies conducted in Uruguay<sup>56</sup> and in Italy,<sup>67</sup> which reported RRs for the highest level of intake of total flavonoids of 0.8 and 0.56, respectively. In particular, in the Italian study a significant inverse association was found for flavanones (RR = 0.51) and flavonols (RR = 0.62) (Table 2). For other classes of flavonoids (including isoflavones, anthocyanidins, flavan-3-ols, and flavones) the estimates were below unity, but not significant.<sup>67</sup>

### Discussion

Epidemiological studies conducted in various populations reported an inverse association between intake of fruit and vegetables and the risk of cancer of the oral cavity and pharynx. The beneficial effect of vegetables and fruit has been attributed to several micronutrients, as well as flavonoids, other polyphenols, and fibers, which have also shown favorable effects on the risk of this cancer. These components display both complementary and overlapping mechanisms of action, including antioxidant effects, binding and dilution of carcinogens in the digestive tract.<sup>68–71</sup> However, data on the relation with single nutrients or food components are more limited and less consistent than those for fruit and vegetables. The protective effect of plant foods may thus result from a combination of different nutrients. It is also possible that a more frequent consumption of fruit and vegetables is a non-specific indicator of a more affluent and better-planned diet.<sup>72</sup> Moreover, although in most studies the inverse association for fruit and vegetables remained significant after adjusting for the two major recognized risk factors for oral and pharyngeal cancer (i.e., tobacco and alcohol) at least part of the protective effect may be explained by some residual confounding. Smokers, for instance, have been re-

ported to consume less vegetables than non smokers,<sup>73</sup> and heavy alcohol drinkers tend to have a limited intake of other more beneficial foods and consequently of essential nutrients.<sup>74,75</sup>

The relation between cereals and oral and pharyngeal cancer risk may depend on the degree to which these products are refined. Compared with refined grains, whole grains are rich in soluble and insoluble fibers, which have been inversely related to the risk.<sup>15,17,24,25,55,76</sup> Moreover, whole grain cereals share several micronutrients and other components with fruit and vegetables, including antioxidant vitamins, polyphenols and lignans.<sup>59,77</sup> Refined cereals and sugars also have a higher rate of absorption than do whole grain cereals, thus causing glycemic overload and compensatory increases in blood insulin level, and consequently in insulin-like growth factor I (IGF-I), which is a potential mutagenic stimulant of tumor cell growth in vitro.<sup>78,79</sup> Glycemic index and load – indicators of the rate of absorption of carbohydrates, and hence a measure of insulin demand – have indeed been directly associated to the risk of oral and pharyngeal cancer in an Italian multicentric study.<sup>80</sup>

Meat consumption has been related to an increased risk of oral and pharyngeal cancer in some – though not all – studies.<sup>81</sup> This effect can be attributed to its content of fats and cholesterol, but other nutrients or compounds may be responsible for the increased risk, including heterocyclic amines, results from cooking, found to be associated with the risk of several neoplasms.<sup>82</sup>

Fish, on the other hand, has been suggested to have a beneficial role on oral and pharyngeal cancer, possibly on account of its high content of *n*–3 fatty acids, which have been shown to have a chemopreventive role on various other neoplasms.<sup>83</sup>

The evidence on the role of milk and dairy products, as well as coffee and tea, on the risk of cancer of the oral cavity and pharynx is scanty, and does not indicate any consistent association.

Thus, fruit and vegetables appear to be the most consistent favorable dietary aspect on oral and pharyngeal neoplasm. In a network of studies from Italy, about 20–25% of cancers of the oral cavity and pharynx were attributed to low fruit and vegetable consumption, and the population attributable risk, rose to 85–95% when tobacco and alcohol consumption were also considered.<sup>69</sup>

### Conflict of interest

None declared.

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