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The role of a Mediterranean diet on the risk of oral and pharyngeal cancer

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Background: The Mediterranean diet has a beneficial role on various neoplasms, but data are scanty on oral cavity and pharyngeal (OCP) cancer.

Methods: We analysed data from a case-control study carried out between 1997 and 2009 in Italy and Switzerland, including 768 incident, histologically confirmed OCP cancer cases and 2078 hospital controls. Adherence to the Mediterranean diet was measured using the Mediterranean Diet Score (MDS) based on the major characteristics of the Mediterranean diet, and two other scores, the Mediterranean Dietary Pattern Adherence Index (MDP) and the Mediterranean Adequacy Index (MAI).

Results: We estimated the odds ratios (ORs), and the corresponding 95% confidence intervals (CI), for increasing levels of the scores (i.e., increasing adherence) using multiple logistic regression models. We found a reduced risk of OCP cancer for increasing levels of the MDS, the ORs for subjects with six or more MDS components compared with two or less being 0.20 (95% CI 0.14–0.28, *P*-value for trend <0.0001). The ORs for the highest *vs* the lowest quintile were 0.20 (95% CI 0.14–0.28) for the MDP score (score 66.2 or more *vs* less than 57.9), and 0.48 (95% CI 0.33–0.69) for the MAI score (score value 2.1 or more *vs* value less 0.92), with significant trends of decreasing risk for both scores. The favourable effect of the Mediterranean diet was apparently stronger in younger subjects, in those with a higher level of education, and in ex-smokers, although it was observed in other strata as well.

Conclusions: Our study provides strong evidence of a beneficial role of the Mediterranean diet on OCP cancer.

The Mediterranean diet is typical of selected area of countries of the Mediterranean basin—including Italy, Southern France, Greece, Spain, and Morocco—and it is characterised by some common features, that is, frequent consumption of varied vegetables and fruit, cereals, fish and seafood, use of olive oil as the main seasoning fat, moderate alcohol consumption, and relatively low consumption of meat and dairy products (Trichopoulou and Lagiou, 1997). The Mediterranean diet has been reported to reduce the risk of cardiovascular disease (Sofi *et al*, 2010; Dilis *et al*, 2012; Misirli *et al*, 2012; Estruch *et al*, 2013) and overall mortality (Trichopoulou *et al*, 1995, 2003; Knoops *et al*, 2004; Mitrou *et al*, 2007; Sofi *et al*, 2010), and to have a favourable role on various common cancers as well (Bosetti *et al*, 2003; Pelucchi *et al*, 2009; Verberne *et al*, 2010; Bamia *et al*, 2013; Couto *et al*, 2013).

Several epidemiological studies investigated the role of single food items characteristic of the Mediterranean diet on oral cavity and pharyngeal (OCP) cancer risk and reported that high intakes of vegetables, foods containing carotenoids, and fruit in general are protective against this neoplasm (World Cancer Research Fund and American Institute for Cancer Research, 2007; Lucenteforte *et al*, 2009). To our knowledge, only two studies have considered the overall role of the Mediterranean diet on OCP cancer (Bosetti *et al*, 2003; Samoli *et al*, 2010). A previous Italian study (Bosetti *et al*, 2003), based on a different data set, considered cancers of the upper aerodigestive tract (UADT), that is, oral cavity, pharynx, oesophagus, and larynx, in relation to adherence to the Mediterranean diet using an *a priori* Mediterranean Diet Score (MDS), and reported an odds ratio (OR) of 0.40 for six or more

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components of the MDS, compared with less than three components. In a case-control study from Greece (Samoli *et al*, 2010) conducted in the context of the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study, a closer adherence to the Mediterranean diet—as measured by the MDS score—was associated with a significant decrease risk of UADT (OR = 0.70 for a two-unit increase in the MDS score), whereas after mutual adjustment, no individual dietary component was significantly associated with the risk.

With the aim of adding further epidemiological data on the issue, we investigated the association between the Mediterranean diet and the OCP risk, using data from a case-control study conducted in Italy and French-speaking Switzerland. To measure the adherence to the Mediterranean diet, we used three different *a priori* defined scores proposed in the literature to combine various foods and food groups, and adopted in various other epidemiological studies (Bach *et al*, 2006).

MATERIALS AND METHODS

Participants and study design. A case-control study on OCP cancer was conducted between 1997 and 2009 in the greater Milan area, Italy and in the canton of Vaud, Switzerland (Bravi *et al*, 2013). Cases were 768 patients (593 men and 175 women) under age 80 years (median 58 years, range: 22–79 years) with incident, histologically confirmed squamous cell cancers of the OCP (excluding cancers of the lip, salivary glands, and nasopharynx), admitted to major teaching or general hospitals in the areas under investigation. Controls were 2078 subjects (1368 men and 710 women, median age 59 years, range: 19–79 years) with no previous history of cancer, admitted to the same hospitals as cases for acute, non-neoplastic conditions, unrelated to tobacco smoking, alcohol drinking, or long-term dietary modifications. Among controls, 19% were admitted for traumas, 21% for other orthopaedic conditions, 51% for acute surgical conditions, and 9% for other miscellaneous conditions. The proportion of refusals of subjects approached for interview was $<5\%$ in Italy and about 15% in Switzerland. The study protocols were approved by the ethical committees of the hospitals involved according to the regulations at the time of the each study conduction, and all participants gave informed consent to participate.

Data collection. Trained personnel interviewed both cases and controls during their hospital stay using a structured questionnaire, including information on sociodemographic characteristics, anthropometric measures, and selected lifestyle habits (including tobacco smoking and alcohol drinking). Subjects' dietary habits during the 2 years before cancer diagnosis or hospitalisation (for controls) were assessed through a validated (Decarli *et al*, 1996) and reproducible (Franceschi *et al*, 1993) food frequency questionnaire (FFQ). The FFQ included information on weekly consumption of 78 foods and beverages, as well as a range of recipes, that is, the most common ones in the Italian and Swiss diet, grouped into seven sections: (i) bread and cereal dishes (first courses); (ii) meat and other main dishes (second courses); (iii) vegetables (side dishes); (iv) fruit; (v) sweets, desserts and soft drinks; (vi) milk and hot beverages; (vii) alcoholic beverages. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; occasional intake (lower than once a week, but at least once a month) was coded as 0.5 per week. An Italian food composition database, integrated with other sources, was used to estimate nutrient and total energy intake in this study (Salvini *et al*, 1998; Gnagnarella *et al*, 2004).

Dietary scores. We defined an *a priori* MDS on the basis of nine characteristics of the traditional Mediterranean diet, as suggested by Trichopoulou *et al* (1995, 2003): high consumption of cereals (including bread and potatoes), fruit, vegetables, legumes, fish, and high monounsaturated/saturated fatty acid (MUFA/SFA) ratio; low consumption of milk (including dairy products) and meat (including meat products); and moderate alcohol intake. For all components, as cutoff point we used the median sex-specific values among controls. For each study subject and each component, a value of one was attributed if the subject was in the component category characteristic of the Mediterranean diet and a value of zero otherwise: thus, for meat/meat products and milk/dairy products a value of 1 was given for low consumption (below the median); for other food items a value of one was given for high consumption (above the median); and for alcohol, a value of one was given for moderate consumption (over 0 and below the median). The MDS score was defined as the sum of the nine individual binary components obtained, and ranged therefore between zero (no adherence) and nine (maximum adherence).

Two additional scores of adherence to the Mediterranean diet were applied: the Mediterranean Dietary Pattern Adherence Index (MDP) (Sanchez-Villegas *et al*, 2002) and the Mediterranean Adequacy Index (MAI) (Alberti-Fidanza and Fidanza, 2004). The MDP was calculated by summing up the standardised residuals of the regression of cereals, fruit, vegetables, legumes, moderate alcohol, MUFA/SFA ratio on total calories, and subtracting those of milk and meat. The MDP was then expressed as a percentage of adherence using the range of the values in the sample, and assumed values between 0 (low adherence) and 100 (maximum adherence) (Sanchez-Villegas *et al*, 2002). MAI was calculated by dividing the sum of the intake of selected typical Mediterranean foods (i.e., bread, cereals, fruit, vegetables, legumes, potatoes, fish, red wine, and vegetable oils) as a percentage of total energy by the sum of the intake of non-typical Mediterranean foods (i.e., milk, cheese, meat, eggs, animal fats and margarines, sweet beverages, cakes, pies and cookies, and sugar) again as the percentage of total energy (Alberti-Fidanza and Fidanza, 2004). In our population, this score ranged between 0.29 and 35.36 units. The three different MDSs were positively correlated: the Spearman correlation coefficients were 0.71 between MDS and MDP, 0.56 between MDS and MAI, and 0.71 between MDP and MAI.

Statistical analysis. We estimated the OR, and corresponding 95% confidence interval (CI), of OCP cancer for categories of the three scores by unconditional multiple logistic regression models (Breslow and Day, 1980), including terms for age (category, quinquennia), sex (category), study center (category, Italy and Switzerland), year of interview (continuous), years of education (category, <7, $7\text{–}<12$, $\geqslant 12$), body mass index (BMI, category, <20, $20\text{–}<25$, $25\text{–}<30$, $\geqslant 30\,\mathrm{kg\,m^{-2}}$), tobacco smoking (category, never, ex-smoker, and current smoker of <15, $15\text{–}<25$, or $\geqslant 25$ cigarettes per day), and total energy intake categories (category, quintiles). We also computed continuous ORs, for an increment of one unit for the MDS and MAI and of 10 units for the MDP.

To investigate whether the association with the three dietary scores was homogeneous across strata of selected covariates, we conducted analyses stratified by age, sex, education, BMI, tobacco smoking, and alcohol drinking. Heterogeneity across strata was tested by likelihood ratio tests and resulting χ^2-statistics.

RESULTS

Table 1 shows the distribution of cases and controls according to centre, sex, age, education, smoking status, alcohol consumption, and BMI. Cases and controls had similar distribution by center and education; cases were more frequently male, had a lower BMI, and were more frequently heavily exposed to tobacco smoking and alcohol drinking than controls.

Table 1. Distribution of 768 cases of oral and pharyngeal cancer and 2078 controls according to sex, age, education, and other selected variables. Italy and Switzerland, 1997–2009

	Cases		Controls	
Characteristic	***N***	**%**	***N***	**%**
Center				
Italy	348	45.3	1001	48.2
Switzerland	420	54.7	1077	51.8
Sex				
Men	593	77.2	1368	65.8
Women	175	22.8	710	34.2
Age (years)				
<50	120	15.6	483	23.2
50–<60	311	40.5	607	29.2
60–<70	238	31.0	645	31.0
⩾70	99	12.9	343	16.5
Education[a] (years)				
<7	143	18.6	379	18.3
7–<12	278	36.2	641	31.0
⩾12	347	45.2	1048	50.7
Body mass index (kg m^{-2})				
<20	98	12.8	107	5.2
20–<25	356	46.4	780	37.5
25–<30	248	32.3	944	45.4
⩾30	66	8.6	247	11.9
Smoking status[a]				
Never smoker	115	15.1	1031	49.7
Ex-smoker	134	17.6	478	23.0
Current smoker				
<15 cigarettes per day	41	5.4	211	10.2
15–24 cigarettes per day	181	23.7	288	13.9
⩾25 cigarettes per day	292	38.3	67	3.2
Alcohol consumption (drinks per day)				
<2	168	21.9	1464	70.5
2–<4	165	21.5	450	21.7
4–<8	205	26.7	141	6.8
⩾8	230	30.0	23	1.1

[a]The sum does not add up to the total because of some missing values.

Table 2 shows the median weekly consumption of nine food items included in the MDS score among male and female controls, and the corresponding ORs for OCP cancer. A significant reduced risk was observed for high *vs* low intake of vegetables (OR = 0.47; 95% CI 0.37–0.60), fruit (OR = 0.68; 95% CI 0.53–0.87), and MUFA/SFA ratio (OR = 0.66; 95% CI 0.51–0.84), and for moderate *vs* non- or heavy drinking of alcoholic beverages (OR = 0.23; 95% CI 0.18–0.29). No significant associations were found for high *vs* low consumption of cereals and potatoes (OR = 0.90), legumes (OR = 1.12), and fish (OR = 1.01), and for low *vs* high consumption of meat and meat products (OR = 0.81), and milk and dairy products (OR = 1.03).

The distribution of OCP cancer cases and controls, and the corresponding ORs according to the MDS, the MDP, and the MAI scores are given in Table 3. A reduced trend in risk was found for increasing levels of the MDS, the ORs for six or more

Table 2. Odds ratios (OR) and 95% corresponding confidence intervals (CI) for oral and pharyngeal cancer among 768 cases and 2078 controls, according to nine items included in the Mediterranean diet score. Italy and Switzerland, 1997–2009

	Median intake[a] (portions per week)		
Components	**Men**	**Women**	**OR[b] (95% CI)**
Vegetables	11.0	11.5	0.47 (0.37–0.60)
Fruit	16.8	21.5	0.68 (0.53–0.87)
Meat and meat products	7.2	5.5	0.81 (0.64–1.04)
Legumes	0.5	0.5	1.12 (0.88–1.43)
Cereals and potatoes	20.9	19.8	0.90 (0.68–1.18)
Milk and dairy products	7.1	10.3	1.03 (0.81–1.31)
Fish	1.7	1.5	1.01 (0.80–1.26)
Alcoholic beverages	0.9	0.0	0.23 (0.18–0.29)
Monounsaturated/saturated fat ratio	1.3	1.4	0.66 (0.51–0.84)

Estimates for binary contrasts, that is, moderate consumption *vs* no/high consumption of alcohol, for low *vs* high consumption of meat/meat products and milk/dairy products, and for high *vs* low consumption of other items.
[a]Median portion per week among controls.
[b]Estimates from unconditional logistic regression models adjusted for sex, quinquennia of age, study center, year of interview, education, tobacco smoking, alcohol drinking, body mass index, and total energy intake.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for oral and pharyngeal cancer among 768 cases and 2078 controls[a] according to the Mediterranean Diet Score (MDS), the Mediterranean Dietary Pattern Adherence Index (MDP), and the Mediterranean Adequacy Index (MAI). Italy and Switzerland, 1997–2009

	Cases *N* (%)	Controls *N* (%)	OR[b] (95% CI)
MDS			
0–2	210 (27.34)	208 (10.01)	1.00[c]
3	152 (19.79)	311 (14.97)	0.46 (0.33–0.65)
4	168 (21.88)	408 (19.63)	0.45 (0.32–0.63)
5	111 (14.45)	455 (21.90)	0.26 (0.18–0.38)
6–9	127 (16.54)	696 (33.49)	0.20 (0.14–0.28)
P-value for trend			<0.0001 0.73 (0.68–0.78)[b,d]
MDP			
0–57.85	328 (42.71)	242 (11.65)	1.00[c]
57.86–60.66	138 (17.97)	431 (20.74)	0.30 (0.22–0.41)
60.67–63.15	101 (13.15)	468 (22.52)	0.23 (0.17–0.32)
63.16–66.16	93 (12.11)	475 (22.86)	0.21 (0.15–0.30)
66.17–100	108 (14.06)	462 ((22.23)	0.20 (0.14–0.28)
P-value for trend			<0.0001 0.33 (0.26–0.41)[b,e]
MAI			
0.29–0.91	237 (30.86)	332 (15.98)	1.00[c]
0.92–1.21	142 (18.49)	428 (20.60)	0.53 (0.38–0.72)
1.22–1.56	125 (16.28)	443 (21.32)	0.50 (0.36–0.69)
1.57–2.09	134 (17.45)	436 (20.98)	0.55 (0.39–0.78)
2.10–35.36	130 (16.93)	439 (21.13)	0.48 (0.33–0.69)
P-value for trend			0.0005 0.90 (0.79–1.03)[b,d]

[a]The sum does not add up to the total because of some missing values.
[b]Estimates from logistic regression model adjusted for sex, quinquennia of age, study center, year of interview, education, tobacco smoking, body mass index, and total energy intake.
[c]Reference category.
[d]OR for an increase of 1 unit.
[e]OR for an increase of 10 units.

Table 4. Odds ratios (OR) and 95% confidence intervals (CI) of oral and pharyngeal cancer among 768 cases and 2078 controls according to the Mediterranean Diet Score (MDS), the Mediterranean Dietary Pattern Adherence Index (MDP), and the Mediterranean Adequacy Index (MAI) in strata of selected covariates. Italy and Switzerland, 1997–2009

		OR (95% CI)[a]		
	Cases/controls	MDS[b]	MDP[c]	MAI[b]
Age				
<60	431/1090	0.67 (0.61–0.73)[d]	0.25 (0.18–0.34)[d]	0.76 (0.62–0.93)[d]
⩾60	337/988	0.80 (0.73–0.87)	0.43 (0.32–0.58)	0.99 (0.86–1.12)
Sex				
Men	593/1368	0.73 (0.68–0.79)	0.29 (0.23–0.38)	0.94 (0.81–1.09)
Women	175/710	0.72 (0.64–0.81)	0.45 (0.30–0.67)	0.77 (0.59–1.01)
Education (years)				
<7	143/379	0.85 (0.74–0.97)[d]	0.75 (0.49–1.17)[d]	1.06 (0.95–1.18)[d]
⩾7	625/1689	0.70 (0.65–0.75)	0.25 (0.19–0.32)	0.74 (0.61–0.88)
Tobacco smoking				
Never smoker	115/1031	0.87 (0.78–0.98)[d]	0.59 (0.39–0.92)[d]	0.84 (0.63–1.10)[d]
Current smoker	514/566	0.73 (0.65–0.83)	0.42 (0.29–0.63)	1.02 (0.87–1.19)
Ex-smoker	134/478	0.64 (0.58–0.71)	0.22 (0.16–0.30)	0.79 (0.65–0.97)
Body mass index (kg m^{-2})				
<25	454/887	0.70 (0.64–0.76)	0.32 (0.24–0.43)	0.91 (0.76–1.08)
⩾25	314/1191	0.76 (0.70 0.84)	0.33 (0.25–0.45)	0.89 (0.74–1.07)

[a]Estimates from logistic regression model adjusted for sex, quinquennia of age, study center, year of interview, education, tobacco smoking, body mass index, and total energy intake.
[b]OR for an increase of 1 unit.
[c]OR for an increase of 10 units.
[d]*P* for heterogeneity <0.05.

MDS components compared with two or less being 0.20 (95% CI 0.14–0.28, *P* for trend *P*<0.0001). Similarly, we observed a significant inverse association for increasing quintiles of the two other scores: the OR for the highest *vs* the lowest quintile was 0.20 (95% CI 0.14–0.28) for the MDP score (score value 66.2 or more *vs* less than 57.9), and 0.48 (95% CI 0.33–0.69) for the MAI score (score value 2.1 or more *vs* value less 0.92). The continuous OR was 0.73 (95% CI 0.68–0.78) for a unit increment of the MDS, 0.33 (95% CI 0.26–0.41) for an increase of 10 units of the MDP score, and 0.90 (95% CI 0.79–1.03) for a unit increment of the MAI score.

The association between the three scores and cancer of OCP was also analysed in strata of selected covariates (Table 4). Risk estimates were consistent across strata of sex and BMI; the associations were somewhat stronger in younger subjects (below age 60), in those with a higher level of education, and ex-smokers.

DISCUSSION

In the present analysis, we found a strong inverse association between OCP cancer risk and adherence to the Mediterranean diet, as measured by various indexes. This finding is in agreement with those of two previous studies, which investigated the role of the Mediterranean diet on OCP neoplasm (Bosetti *et al*, 2003; Samoli *et al*, 2010). The favourable effect of the Mediterranean diet was apparently stronger in younger subjects, in those with a higher level of education, and in ex-smokers, although it was observed in other strata as well.

A few other epidemiological studies, which analysed the role of diet on UADT cancers, found consistent beneficial effects of *a priori* or *a posteriori* dietary patterns based on fruit and vegetables or nutrients contained in vegetable foods, and a possible unfavourable effect of dietary patterns based on meats and animal products emerged as well (Bravi *et al*, 2012; Chuang *et al*, 2012; Helen-Ng *et al*, 2012; De Stefani *et al*, 2013). In particular, a recent pooled analysis of 22 case-control studies (Chuang *et al*, 2012) within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, using a dietary pattern characterised by high fruit/vegetable and low red meat intake, reported a significant reduced risk of head and neck cancer (OR = 0.90 for an unit increment of the score).

With reference to single-specific components of the Mediterranean diet, fruit and vegetables were associated with a reduced risk of OCP cancer in several case-control studies (Boeing *et al*, 2006; World Cancer Research Fund and American Institute for Cancer Research, 2007; Lucenteforte *et al*, 2009). The protective role of vegetables and fruit in OCP cancer has been attributed to their content of several micronutrients, including carotenoids, vitamin C and E, as well as flavonoids, found to be inversely related to OCP cancer (IARC, 2003; Rossi *et al*, 2007; World Cancer Research Fund and American Institute for Cancer Research, 2007).

In Mediterranean countries, olive oil is largely consumed and is the main source of monounsaturated fats. Olive oil has been shown to have a favourable influence on various neoplasms, including OCP cancer (Pelucchi *et al*, 2009), possibly on account of its antioxidant properties attributable both to oleic acid itself and to the presence of other nutrients, such as vitamin E and polyphenols (Owen *et al*, 2000).

A beneficial effect of fish intake on OCP cancer has been suggested by several studies (Fernandez *et al*, 1999), but a few other studies provided direct or null associations (World Cancer Research Fund and American Institute for Cancer Research, 2007; Lucenteforte *et al*, 2009).

Meat consumption has been related to an increased risk of OCP cancer, although not all studies provided consistent results (Sapkota *et al*, 2008; Aune *et al*, 2009; Lucenteforte *et al*, 2009; Chuang *et al*, 2012; Steffen *et al*, 2012). The unfavourable role of meat on cancers of the UADT has been attributed to its fatty-acid composition and the presence of nitrites, *N*-nitroso compounds, heterocyclic amines, and polycyclic aromatic hydrocarbons (Phillips, 1999; Zheng and Lee, 2009), although the issue remains unsettled.

The evidence on the role of other dietary items including milk, dairy products, cereals, and sugars on OCP cancer is inconsistent, with several studies reporting both direct and inverse relationships (World Cancer Research Fund and American Institute for Cancer Research, 2007; Peters *et al*, 2008; Sapkota *et al*, 2008; Lucenteforte *et al*, 2009).

High alcohol consumption is strongly associated with cancers of the upper digestive and respiratory tract (IARC, 2010), whereas for moderate consumption, particularly of red wine, the risk is limited, if any (Bagnardi *et al*, 2013).

In addition to the role of any single component considered, the value of this work is to definitely establish and quantify the favourable impact of the Mediterranean diet on OCP cancer, for which scanty epidemiological data are available. This may well explain the relatively lower rates of this neoplasm in the Mediterranean, as compared with central Europe (Bosetti *et al*, 2013; La Vecchia *et al*, 2014).

Limitations of our study include possible recall and selection bias (Breslow and Day, 1980). OCP cancer cases may have changed their diet owing to the disease, although we investigated dietary habits 2 years before cancer diagnosis. Dietary habits of hospital controls may not be representative of the general population, although we selected controls among patients with acute conditions not associated with long-term dietary modifications, and we excluded all diagnoses that might have been associated with tobacco smoking and alcohol drinking. Moreover, information from hospital patients has been shown to be satisfactory reproducible (D'Avanzo *et al*, 1997). The high participation rate among cases and controls is reassuring against a major role of selection bias. Among the strengths of the study, there are its large sample size, the comparable catchment areas of study subjects, the reproducibility and validity of dietary information, and the allowance for a large number of covariates.

Adherence to the Mediterranean diet was measured using different *a priori* scores proposed in the literature, that is, the MDS (Trichopoulou *et al*, 1995), the most commonly used index from epidemiological studies, and two additional scores, the MDP (Sanchez-Villegas *et al*, 2002) and the MAI (Alberti-Fidanza and Fidanza, 2004). These three scores present a few differences: the MDS and the MDP scores, apart from fish, included the same food items; the MAI score on the other end integrated other food items, that is, eggs, sugar, and sweet foods. The three scores, in any case, gave consistent associations, providing a strong evidence of a beneficial role of the Mediterranean diet on OCP cancer.

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