Selected Micronutrient Intake and the Risk of Gastric Cancer[1]

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Abstract

The relationship between intake of selected micronutrients and gastric cancer risk was investigated using data from a case-control study conducted in Italy between 1985 and 1992 on 723 cases of histologically confirmed, incident gastric cancer, and 2024 controls hospitalized for acute, nonneoplastic, nondigestive tract diseases. Relative risks of subsequent quintiles of intake were computed after allowance for sex, age, and other major identified potential confounding factors, including an estimate of total calorie intake. No trend in risk emerged for intake of retinol, vitamin D and vitamin E, whereas a protective pattern was observed for consumption of beta-carotene, ascorbic acid, folate, and nitrates, with risk estimates for the highest intake quintiles of 0.27, 0.40, 0.58, and 0.43, respectively. Significant direct trends in risk were found for methionine, calcium, and nitrites. When the effect of various micronutrients was taken into account, a residual protective effect was observed for beta-carotene and ascorbic acid, and a direct association with methionine remained, whereas the protective effect of folates and nitrates and the direct associations of nitrites were no longer evident. The risk estimates for the upper quintiles of beta-carotene, ascorbic acid, and methionine consumption were respectively 0.38, 0.53, and 2.40, and all the trends in risk were significant and consistent across strata of sex and age. Whether this reflects a specific effect of these micronutrients, rather than problems of collinearity or other limitations of the data, is open for discussion. Nonetheless, these data indicate that selected micronutrients may have an impact in the process of gastric carcinogenesis.

Introduction

Dietary habits are important determinants of gastric cancer, and improvements in diet have been associated with a general decline of gastric cancer and related mortality (1). The precise components of diet which may have some impact on gastric carcinogenesis are, however, still largely undefined. Most studies based on food items found protective effects of fresh fruits and vegetables, while preserved meat and selected starchy foods—often indicators of a less affluent diet—were associated with increased risk (2–10).

Scanty epidemiological data are, however, available on the role of nutrients, and micronutrients, on gastric cancer risk. There are indications that selected micronutrients with antioxidant effect, such as ascorbic acid, beta-carotene, and α-tocopherol, are protective against gastric carcinogenesis (2, 11–16), while nitrites, which may cause intragastric synthesis of *N*-nitroso compounds, have been associated with increased risk, but their impact on a population level remains open for discussion (14–20). Furthermore, there is a general paucity of systematic efforts to consider simultaneously the role of various micronutrients on gastric carcinogenesis, in order to understand and quantify the separate effect of each factor after allowance for others.

To provide further information on this issue, we have considered the role of selected micronutrients on the risk of stomach cancer, using data from a case-control study conducted in Northern Italy, an area with relatively high gastric cancer rates among developed countries on a worldwide scale (21), previously considered with reference to intake of various foods (4). That analysis showed an association with frequent consumption of starchy foods typical of the traditional diet and protections from fresh fruits and vegetables. The question arises, therefore, of whether there is an influence of specific micronutrients on gastric carcinogenesis.

Subjects and Methods

Data were derived from an ongoing case-control study conducted in the major teaching and general hospitals in the Greater Milan area since 1985. The present analyses are based on data collected until December 1992. The general design of the study has been previously described (4). Briefly, trained interviewers identified and questioned cases of gastric cancer and controls admitted to hospital in the area under surveillance for nonneoplastic, nondigestive tract diseases, not related to long-term modifications of diet.

The standard questionnaire included questions about sociodemographic and anthropometric characteristics, a problem-oriented medical history, family history of gastric and colorectal cancers, and information about the frequency of consumption of 29 indicator foods. These items included major sources of beta-carotene, retinol; vitamins C, D, and E; folate; methionine and calcium; and nitrites and nitrates. From these items, the nutrient intake was computed by multiplying the frequency of intake of each unit of food by the nutrient content of a standard average portion. Micronutrient values were derived from Italian tables of food composition (22), integrated by other sources,

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Table 1 Distribution of 723 stomach cancer cases and 2024 controls according to socio-demographic variables. Milan, Italy, 1985–1992

Variable	Stomach cancer		Controls	
	No.	(%)	No.	(%)
Sex				
Males	443	(61.3)	1189	(58.7)
Females	280	(38.7)	835	(41.3)
Age (yr)				
<50	123	(17.0)	687	(33.9)
50–59	205	(28.4)	593	(29.3)
60–69	284	(39.3)	588	(29.1)
70–74	111	(15.4)	156	(7.7)
Education (yr)				
<7	465	(64.3)	986	(48.7)
7–11	170	(23.5)	591	(29.2)
≥12	88	(12.2)	447	(22.1)

when required (23). The questionnaire was restricted to the frequency of consumption of a limited number of selected food items, with no information on portion size. Thus, the measures obtained should be considered only approximations of the real values. Subjects were classified by quintile of intake of each nutrient on the basis of the consumption of controls.

Cases. Cases were 723 subjects (443 males and 280 females) with a histologically confirmed stomach cancer diagnosed no later than 1 year before interview, admitted to the National Cancer Institute and to the Ospedale Maggiore of Milan, including the four largest teaching and general hospitals of the Greater Milan area. The age range was 19–74 years (median age, 61).

Controls. Controls were 2024 subjects, including 1189 males and 835 females, aged 19–74 years (median age, 55). They were admitted to the same network of hospitals where cases were identified for acute, nonneoplastic and nondigestive tract diseases, divided into various diagnostic categories: 47% were admitted for traumatic diseases; 20% for nontraumatic orthopedic diseases; 19% for acute surgical conditions; and 14% for other miscellaneous disorders, such as acute infections, skin, eye, ear, nose, and throat conditions.

Over 80% of cases and controls came from the same region, Lombardy, and over 90% came from Northern Italy. Participation was over 95% for both cases and controls.

Data Analysis. OR[3], as estimators of relative risks, with the corresponding 95% CI, of gastric cancer were computed for various nutrients considered, derived from data stratified for sex and age by the Mantel-Haenszel procedure (24, 25). In order to control for other identified potential confounding factors, unconditional multiple logistic regression was used, with maximum likelihood fitting (24, 25). All the regression equations included terms for sex, age, education, body mass index, and family history of gastric cancer, plus, when specified, estimated total calorie intake. Furthermore, allowance was made for all nutrients significantly related to gastric cancer after the previous analyses. For multiple levels of exposure, the significance of the linear trends in risk was assessed by comparing the difference between the deviances of the model without and with a term continuous for each nutrient to the χ^2 distribution with 1 degree of freedom.

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 Distribution of 723 cases of stomach cancer and 2024 controls according to quintiles (defined on the distribution of controls) of intake of selected micronutrients. Milan, Italy, 1985–1992

	Quintiles				
	1° (lowest)	2°	3°	4°	5° (highest)
Beta-carotene (μg/die)					
Upper limits	2268.0	2876.7	3608.7	5608.7	
No. of controls	398	387	436	415	388
No. of stomach cancer cases	214	165	144	132	68
Retinol (μg/die)					
Upper limits	1053.7	3990.0	4774.0	5368.0	
No. of controls	406	404	403	404	407
No. of stomach cancer cases	120	160	127	170	146
Ascorbic acid (mg/die)					
Upper limits	79.67	104.67	128.00	157.00	
No. of controls	403	407	405	406	403
No. of stomach cancer cases	258	154	125	94	92
Vitamin D (μg/die)					
Upper limits	0.79	1.14	1.47	1.97	
No. of controls	400	412	405	401	406
No. of stomach cancer cases	118	140	174	145	146
Vitamin E (mg/die)					
Upper limits	3.87	4.63	5.33	6.26	
No. of controls	405	405	405	404	405
No. of stomach cancer cases	159	145	127	137	155
Folate (μg/die)					
Upper limits	162.63	195.65	225.80	261.49	
No. of controls	405	404	405	406	404
No. of stomach cancer cases	186	153	129	127	128
Methionine (mg/die)					
Upper limits	1377.1	1594.3	1807.1	2039.0	
No. of controls	404	406	404	406	404
No. of stomach cancer cases	98	128	136	149	212
Calcium (mg/die)					
Upper limits	468.1	642.1	842.1	1029.7	
No. of controls	405	405	405	405	404
No. of stomach cancer cases	105	139	145	151	183
Nitrites (mg/die)					
Upper limits	1.91	2.41	2.94	3.64	
No. of controls	405	404	405	406	404
No. of stomach cancer cases	123	128	126	153	193
Nitrates (mg/die)					
Upper limits	62.95	80.70	96.33	116.88	
No. of controls	405	405	404	406	404
No. of stomach cancer cases	228	156	117	117	105

Results

The distribution of cases and controls according to sex, age, and education is shown in Table 1. Cases and controls

Table 3 Relative risk estimates (and 95% confidence intervals) of stomach cancer in relation to selected micronutrient intake. Milan, Italy, 1985–1992[a]

Quintile of intake	MH[b]	MLR[c]	Quintile of intake	MH[b]	MLR[c]
Beta-carotene			Folate		
2°	0.78 (0.61–1.01)	0.80 (0.61–1.04)	2°	0.89 (0.69–1.16)	0.82 (0.62–1.08)
3°	0.60 (0.46–0.77)	0.59 (0.45–0.78)	3°	0.79 (0.60–1.04)	0.71 (0.53–0.96)
4°	0.61 (0.47–0.79)	0.54 (0.41–0.72)	4°	0.81 (0.62–1.07)	0.59 (0.43–0.80)
5° (highest)	0.33 (0.24–0.45)	0.27 (0.19–0.38)	5° (highest)	0.84 (0.64–1.11)	0.58 (0.42–0.80)
P (trend)	<0.001	<0.001	*P* (trend)	NS	<0.001
Retinol			Methionine		
2°	1.36 (1.03–1.80)	1.24 (0.93–1.67)	2°	1.35 (1.00–1.82)	1.31 (0.95–1.81)
3°	1.07 (0.80–1.43)	0.99 (0.74–1.34)	3°	1.36 (1.01–1.84)	1.27 (0.91–1.76)
4°	1.38 (1.05–1.82)	1.21 (0.91–1.62)	4°	1.58 (1.18–2.13)	1.52 (1.08–2.14)
5° (highest)	1.17 (0.88–1.55)	0.94 (0.70–1.27)	5° (highest)	2.46 (1.85–3.28)	2.07 (1.45–2.94)
P (trend)	NS[d]	NS	*P* (trend)	<0.001	<0.001
Ascorbic Acid			Calcium		
2°	0.61 (0.48–0.79)	0.61 (0.47–0.79)	2°	1.23 (0.92–1.65)	1.15 (0.85–1.51)
3°	0.54 (0.42–0.70)	0.52 (0.40–0.68)	3°	1.38 (1.03–1.86)	1.26 (0.92–1.71)
4°	0.42 (0.32–0.56)	0.41 (0.31–0.55)	4°	1.33 (1.00–1.78)	1.24 (0.91–1.68)
5° (highest)	0.44 (0.33–0.58)	0.40 (0.30–0.55)	5° (highest)	1.71 (1.29–2.26)	1.41 (1.03–1.92)
P (trend)	<0.001	<0.001	*P* (trend)	<0.001	<0.05
Vitamin D			Nitrites		
2°	1.18 (0.89–1.57)	1.19 (0.88–1.60)	2°	1.10 (0.83–1.48)	0.98 (0.72–1.33)
3°	1.48 (1.12–1.95)	1.45 (1.08–1.93)	3°	1.13 (0.84–1.52)	0.99 (0.72–1.36)
4°	1.29 (0.97–1.71)	1.29 (0.96–1.74)	4°	1.44 (1.08–1.92)	1.15 (0.84–1.59)
5° (highest)	1.32 (0.99–1.76)	1.35 (1.00–1.83)	5° (highest)	1.90 (1.43–2.52)	1.35 (0.96–1.88)
P (trend)	<0.05	<0.05	*P* (trend)	<0.001	<0.05
Vitamin E			Nitrates		
2°	0.96 (0.74–1.26)	0.91 (0.68–1.21)	2°	0.69 (0.53–0.88)	0.64 (0.49–0.83)
3°	0.91 (0.69–1.21)	0.75 (0.54–1.03)	3°	0.55 (0.42–0.72)	0.50 (0.38–0.67)
4°	1.05 (0.80–1.39)	0.83 (0.60–1.16)	4°	0.59 (0.45–0.77)	0.52 (0.39–0.70)
5° (highest)	1.26 (0.96–1.66)	0.88 (0.62–1.24)	5° (highest)	0.54 (0.41–0.71)	0.43 (0.32–0.59)
P (trend)	NS	NS	*P* (trend)	<0.001	<0.001

[a] Reference category is the lowest quintile of intake.
[b] Mantel-Haenszel estimates adjusted for age in decades and sex.
[c] Estimates from multiple logistic regression equations including terms for age, sex, education, family history of gastric cancer, body mass index, and total energy intake.
[d] NS, not significant.

tended to differ with respect to years of education, with controls being significantly more educated than cases.

Table 2 shows the distribution of cases and controls according to quintile of intake of 10 selected micronutrients or substances. Apparent differences in the distribution emerged for beta-carotene, ascorbic acid, folate, methionine, calcium, and nitrates, with a lower frequency of cases in the highest quintiles of intake, as well as for calcium and methionine, with a lower frequency of cases in the lowest quintiles.

The corresponding ORs are shown in Table 3. No trend in risk emerged for intake of retinol (OR, 0.94; 95% CI, 0.70–1.27, for the highest consumption quintile), vitamin D (OR, 1.35; 95% CI, 1.00–1.83) and vitamin E (OR, 0.88; 95% CI, 0.62–1.24), whereas a protective pattern was observed for consumption of beta-carotene, ascorbic acid, folate, and nitrates, with relative risk estimates of 0.27 (95% CI, 0.19–0.38), 0.40 (95% CI, 0.30–0.55), 0.58 (95% CI, 0.42–0.80), and 0.43 (95% CI, 0.32–0.59), respectively. Significantly increased risks according to level of consumption of methionine (OR, 2.07; 95% CI, 1.45–2.94, for the highest intake quintile), calcium (OR, 1.41; 95% CI, 1.03–1.92), and nitrites (OR, 1.35; 95% CI, 0.96–1.88) were found.

All the trends for these variables were significant after controlling for education, family history of gastric cancer, body mass index, and total calorie intake, besides sex and age, in multivariate analysis. However, allowance for calories and other potential confounding factors in multivariate analysis tended to reduce the association with nitrites and to increase the protection for folate.

The correlation matrix for various micronutrients significantly associated to gastric cancer risk is given in Table 4. All the correlation coefficients were positive, but only three of these (*i.e.*, between nitrates, beta-carotene, and ascorbic acid, and between nitrites and methionine) were above 0.5.

In Table 5 relative risk estimates taking simultaneously into account the effect of various micronutrients are presented. A residual protective effect was observed for beta-carotene and ascorbic acid, and the increased risk of gastric cancer associated with methionine remained, resulting in risk estimates of 0.38, 0.53, and 2.40, respectively, whereas the protective effect of folate and nitrates, and the direct association with nitrites were no longer evident after these dietary variables were added to the logistic models.

Relative risk estimates for gastric cancer according to levels of consumption of the three nutrients emerged as the

Table 4 Correlation coefficients between selected micronutrients. Milan, Italy, 1985–1992

	β-carotene	Ascorbic acid	Folate	Methionine	Nitrites	Nitrates
β-carotene	1.00					
Ascorbic acid	0.47	1.00				
Folate	0.23	0.38	1.00			
Methionine	0.33	0.19	0.47	1.00		
Nitrites	0.24	0.09	0.14	0.71	1.00	
Nitrates	0.52	0.62	0.41	0.36	0.24	1.00

Table 5 Multivariate relative risk estimates (95% confidence intervals) of stomach cancer in relation to selected micronutrient intake. Milan, Italy, 1985–1992[a]

Quintile of intake	MLR[b]	*P* (trend)
Beta-carotene		
2°	0.92 (0.70–1.22)	
3°	0.73 (0.55–0.99)	
4°	0.71 (0.52–0.98)	
5° (highest)	0.38 (0.26–0.56)	<0.001
Ascorbic acid		
2°	0.63 (0.49–0.84)	
3°	0.56 (0.41–0.78)	
4°	0.47 (0.32–0.68)	
5° (highest)	0.53 (0.35–0.81)	<0.001
Folate		
2°	1.24 (0.90–1.71)	
3°	1.32 (0.91–1.92)	
4°	1.22 (0.80–1.87)	
5° (highest)	1.33 (0.82–2.18)	NS[c]
Methionine		
2°	1.40 (1.01–1.96)	
3°	1.32 (0.94–1.86)	
4°	1.65 (1.15–2.36)	
5° (highest)	2.40 (1.64–3.51)	<0.001
Nitrites		
2°	0.96 (0.69–1.32)	
3°	0.97 (0.70–1.35)	
4°	1.02 (0.73–1.43)	
5° (highest)	1.12 (0.78–1.59)	NS
Nitrates		
2°	0.71 (0.53–0.96)	
3°	0.66 (0.47–0.92)	
4°	0.78 (0.54–1.12)	
5° (highest)	0.64 (0.43–0.97)	NS

[a] Reference category is the lowest quintile.
[b] Estimates for multiple logistic regression equations including terms for age, sex, education, family history of gastric cancer, body mass index, total energy intake, plus all the above variables.
[c] NS, not significant.

most important determinants of gastric cancer risk (*i.e.*, beta-carotene, ascorbic acid, and methionine) were computed across strata of sex and age (Table 6). The trends in risk were significant and consistent across various strata considered, in the absence of any relevant interaction with these covariates.

Discussion

This study confirms that beta-carotene and ascorbic acid have a protective effect against gastric carcinogenesis. There was also some protection by folate and nitrates, but this was no longer evident after simultaneous inclusion of these factors in a single model with beta-carotene and ascorbic acid. A significant direct association emerged for methionine and nitrite consumption, whereas α-tocopherol, vitamin D, and calcium showed no clear pattern of association with gastric cancer risk.

An earlier study on an Italian population found a protective effect from beta-carotene, vitamin C and E, but no association with retinol and calcium; nitrites were directly and nitrates slightly inversely associated with the risk of gastric cancer (15). In most previous studies, there was, however, little systematic effort to mutually allow for the possible effects of various micronutrients. In a study from Canada (13), vitamin C and nitrates showed some protective effect, and vitamin E showed no association. In a study from Germany (11), the only significant association with gastric cancer, after adjustment for other nutrients, was an inverse one with vitamin C. Nonetheless, other studies found a significantly decreased risk related to intake of vitamin A or beta-carotene (5, 14, 15). In a Spanish study (26), the strongest protection was observed for vitamin C and vitamin A from fruits and vegetables. It appears, therefore, that beta-carotene and ascorbic acid are among the most consistent protective factors against gastric carcinogenesis. This might be related to an antioxidant effect of these vitamins, although the protection is less convincing for other powerful antioxidants, including α-tocopherol. It is also possible, however, that ascorbic acid has a specific antioxidant and antinitrosating effect in the aqueous (but not lipid) phase of gastric juice (27, 28).

Folate has been shown protective against colorectal carcinogenesis (29), but data are scanty on stomach cancer risk. In this population, folate was mainly derived from vegetables. The lack of association in the multivariate analysis may thus simply reflect a strong collinearity between folate and these nutrients, and hence a correlate of protection of beta-carotene and ascorbic acid, or other constituents of vegetables and fruit, as suggested by the absence of residual associations in the model including these nutrients.

These results confirm an increased risk of gastric cancer with nitrite intake, previously found in epidemiological and experimental studies (18), but an inverse association with nitrates. Although carcinogenic *N*-nitroso compounds can be formed from nitrites and nitrates in the gastric lumen, the results from previous studies are not consistent. Still, in general, they do not suggest any strong and general association between dietary intake of nitrites and nitrates and gastric cancer risk on a population level (14–15, 17–20, 30). In this study, the positive association of nitrites (derived essentially from canned meat, bread, and some vegetables) with gastric cancer is explainable through a real contribution of exogenous nitrites to the production of *N*-nitroso compounds or by confounding by other dietary factors. The association became, in fact, weaker and was not significant

Table 6 Relative risk estimates (95% confidence intervals) of stomach cancer in relation to selected micronutrient intake in separate strata of sex and age. Milan, Italy, 1985–1992[a]

Quintile of intake	Sex		Age	
	Males	Females	<60 yr	≥60 yr
Beta-carotene				
2°	1.09 (0.78–1.52)	0.47 (0.29–0.75)	0.72 (0.49–1.06)	0.89 (0.61–1.30)
3°	0.65 (0.45–0.92)	0.51 (0.33–0.79)	0.60 (0.41–0.88)	0.59 (0.40–0.88)
4°	0.48 (0.33–0.69)	0.58 (0.37–0.92)	0.58 (0.40–0.85)	0.49 (0.32–0.75)
5° (highest)	0.36 (0.23–0.57)	0.17 (0.10–0.29)	0.22 (0.13–0.35)	0.32 (0.20–0.52)
P (trend)	<0.001	<0.001	<0.001	<0.001
Ascorbic acid				
2°	0.89 (0.64–1.24)	0.33 (0.21–0.50)	0.53 (0.36–0.78)	0.69 (0.49–0.99)
3°	0.83 (0.59–1.18)	0.24 (0.15–0.38)	0.42 (0.29–0.63)	0.65 (0.44–0.96)
4°	0.48 (0.33–0.72)	0.28 (0.17–0.45)	0.29 (0.19–0.44)	0.59 (0.38–0.91)
5° (highest)	0.12 (0.41–0.90)	0.18 (0.11–0.31)	0.28 (0.18–0.42)	0.61 (0.38–0.96)
P (trend)	<0.001	<0.001	<0.001	<0.01
Methionine				
2°	1.18 (0.76–1.83)	1.53 (0.95–2.45)	1.29 (0.81–2.08)	1.33 (0.86–2.07)
3°	1.50 (0.95–2.35)	1.13 (0.69–1.84)	1.19 (0.71–1.97)	1.36 (0.87–2.11)
4°	1.90 (1.21–2.99)	1.14 (0.66–1.95)	1.69 (1.03–2.77)	1.37 (0.85–2.21)
5° (highest)	2.41 (1.52–3.83)	1.70 (0.96–2.99)	2.27 (1.37–3.75)	1.86 (1.12–3.09)
P (trend)	<0.001	<0.001	<0.001	<0.05

[a] Reference category is the lowest quintile of intake. Estimates for multiple logistic regression equations including terms for age, sex (when required), family history of gastric cancer, body mass index, and total energy intake.

after adjustment for dietary variables. Because nitrates are derived mainly from vegetables (including cabbages and other cruciferae, green salad, tomatoes, peppers, besides bread, beer, and canned meat), their protection is likely to reflect the protection conveyed by beta-carotene and vitamin C and other potential protective factors of a diet rich in fruit and vegetables (4, 31, 32).

Some indirect associations or lack of associations deserve consideration, also. These include the increased risk with increasing methionine consumption, which is derived mainly from legumes and potatoes, and may therefore represent an aspecific indicator of a less affluent diet in this population, and for meat, including ham, veal, chicken, liver, bacon, canned meat, and sausages, and may thus indicate some role of meat, or some of its components, on gastric carcinogenesis (1, 4). The lack of protection by α-tocopherol, if not due to chance or bias, may be due to the levels of intake which can exert some protective effect, whereas there is little evidence that retinol, vitamin D, and calcium are protective against gastric carcinogenesis.

The size of this data set allowed sufficient statistical power to obtain reasonably precise risk estimates and significant trends in risk for several micronutrients. Reliability of the estimated micronutrient intake should be satisfactory. With reference to reproducibility, a companion study (33) gave for nutrients a median correlation coefficients of 0.67, with most values falling between 0.60 and 0.70. As for validity, the comparison with available average recommended daily intake for the Italian population (34) is reassuring with reference to the completeness and reliability of our information, although our estimates were based on the consumption of a restricted number of items.

Cases and controls came from comparable catchment areas (*i.e.,* over 80% come for the same region); and the almost complete participation rate, the similar interview setting for cases and controls, and the allowance for major potential confounding factors, including an estimate of total energy intake (35), are reassuring against selection, information, and confounding bias.

In conclusion, this large case-control study provides support for a protective effect of various micronutrients on gastric cancer risk, which persisted after allowance for several potential confounding factors, including total calorie intake. There was also some indication that nitrites are associated to the risk, but only beta-carotene and ascorbic acid remained significantly protective after simultaneous allowance for various micronutrients. Whether this reflects a more specific or stronger effect of these micronutrients rather than limitations in data collection following collinearity between various factors remains to be clarified in further research.

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