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# Dietary Nitrates, Nitrites, and N-Nitroso Compounds and Cancer Risk: A Review of the Epidemiologic Evidence

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*Experimental animal studies have shown N-nitroso compounds (NOC) to be potent carcinogens. Epidemiologic evidence of the carcinogenic potential of dietary NOC and precursor nitrates and nitrites in humans remains inconclusive with regard to the risk of stomach, brain, esophageal, and nasopharyngeal cancers. Inadequate available data could obscure a small to moderate effect of NOC.*

## Introduction

Various N-nitroso compounds (NOC) have been found to be carcinogenic to multiple organs in at least 40 animal species including higher primates.[1] The cellular and molecular changes induced by some NOC in animals have been shown to be very similar to those in human tissues.[2] In addition to exposure to preformed NOC (e.g., tobacco use, certain occupational environments, diet),[2,3] humans are exposed to nitrogen-containing compounds and nitrosating agents, which can react in vivo to form NOC. Nitrate, nitrite, and nitrosating agents can also be synthesized endogenously in reactions mediated by bacteria and macrophages.[2] The efficacy of certain vitamins as nitrosation inhibitors provides a plausible explanation of epidemiologic findings that have shown a protective effect of fruit and vegetable consumption against various malignancies.[4,5] Despite extensive information regarding carcinogenicity of NOC in animals, there have been few analytic studies investigating the risk in humans, and what is available is limited to case-control studies. This paper reviews the epidemiologic evidence relating estimated dietary intake of NOC, nitrates, and nitrites (and some examples of individual foods rich in these substances) with the risk of stomach, brain, esophageal, and nasopharyngeal cancers.

Vegetables usually contribute 75–80% of the total daily intake of nitrate, with high levels in lettuce, spinach, celery, beetroot, turnip greens, etc. The nitrate concentration of drinking water varies widely depending on the source (high concentrations in private water supplies), season, and proximity to arable land. Nitrate and nitrite are often added as preservatives to processed (cured) meat, meat products, and fish. Nitrites are also found naturally in some grains and vegetables. Nitrosodimethylamine has been found in various processed meats (salted, cured, or smoked) and fish and in beer.[3,6,7]

## Stomach Cancer

Large differences in the incidence of stomach cancer exist worldwide. The highest incidence rates are found in Japan and China; Switzerland and France have intermediate rates; and North America and Greece have the lowest rates. The continuous decline of stomach cancer rates over the past several decades and the results of migrant studies suggest a predominant etiologic role for external environmental factors generally believed to be dietary. A recent review by the American Institute for Cancer Research[8] considers consumption of diets high in vegetables and fruits and low in salt and the use of refrigeration for perishable foods as the most effective means of preventing stomach cancer. An important established nondietary cause of stomach cancer is infection with the *Helicobacter pylori* bacterium. Various other potential risk factors such as high consumption of grilled and barbecued meat and fish and cured meats are discussed. The stomach is an established site for NOC carcinogenesis in animals.[8,9]

Of the six case-control studies that estimated dietary intake of nitrate and its association with stomach cancer risk, three revealed non–statistically significant results[10–13] whereas the other three studies[14–16] found a significant inverse association with stomach cancer. The methods and results of these studies are described in Table 1.[10–17] In the Canadian study of Risch and coworkers,[15] 246 cases of stomach cancer were compared with 246 population-based controls matched by age, sex, and area of residence. The apparent protective effect (odds ratio [OR]=0.66, 95% confidence interval [CI]=0.54–0.81) of dietary intake of

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**Table 1.** Case-Control Studies on Dietary Nitrate, Nitrite, and N-Nitroso Compounds and Risk of Stomach Cancer

| Reference and Number of Cases | Nitrate | Odds Ratio (95% CI)[a] | Nitrite | Odds Ratio (95% CI)[a] | N-Nitrosodimethylamine | Odds Ratio (95% CI)[a] |
|---|---|---|---|---|---|---|
| Canada | | | | | | |
| Risch et al.[15] (*n*=246) | ↓ | 0.66 (0.54–0.81)[b] | ↑ | 2.61 (1.61–4.22)[c] | NS | 0.94 (0.14–6.13)[b] |
| Four areas in Italy | | | | | | |
| Buiatti et al.[10] (*n*=1016) | NS | 0.9 (0.7–1.2)[d] | NS | 1.2 (0.8–1.8)[e] | | |
| Palli et al.[11] (*n*=923) | | | | | | |
| Cardia | NS | 1.1 (0.6–2.3)[f] | NS | 0.9 (0.3–2.7)[g] | | |
| Other gastric cancer | NS | 0.7 (0.6–1.0)[f] | NS | 1.2 (0.8–1.9)[g] | | |
| Sweden | | | | | | |
| Hansson et al.[12] (*n*=338) | NS | 0.97 (0.60–1.59)[h] | NS | 1.22 (0.82–1.81) | | |
| Spain | | | | | | |
| González et al.[16] (*n*=354) | ↓ | 0.45 (*p* trend = 0.007)[i] | NS | 1.28 (*p* trend = 0.377)[i] | Nitrosamine ↑ | 2.09 (*p* trend = 0.007)[i] |
| Greater Milan area | | | | | | |
| La Vecchia et al.[14] (*n*=723) | ↓ | 0.64 (0.43–0.97)[j] | NS | 1.12 (0.78–1.59)[j] | | |
| La Vecchia et al.[17] (*n*=746) | | | | | ↑ | 1.37 (1.1–1.7)[k] |
| France | | | | | | |
| Pobel et al.[13] (*n*=92) | NS | 0.76 (0.38–1.50)[l] | NS | 0.88 (0.44–1.79)[l] | ↑ | 7.00 (1.85–26.46)[l] |

Note: CI=confidence interval. NS=statistically not significant. ↑=statistically significant direct association. ↓=statistically significant inverse association.

[a] Highest intake level vs. lowest.

[b] Adjusted for food consumption and ethnicity.

[c] Model simultaneously includes dietary fiber, nitrite, chocolate, carbohydrates, no refrigeration, total food consumption, ethnicity.

[d] Adjusted for nondietary variables and kilocalories.

[e] Adjusted for kilocalories, nondietary variables, protein, ascorbic acid, ß-carotene, α-tocopherol.

[f] Adjusted for caloric intake, age, sex, area, place of residence, migration from the South, socioeconomic status, familial history, Quetelet index.

[g] Adjusted for [f] plus protein, ascorbic acid, β-carotene, α-tocopherol.

[h] Multivariate analysis including age, gender, ascorbic acid, β-carotene, α-tocopherol, nitrates in the same model.

[i] Adjusted for total calories.

[j] Estimates for multiple logistic regression equations including terms for age, sex, education, family history of gastric cancer, body mass index, total energy intake, β-carotene, ascorbic acid, folate, methionine, nitrate, and nitrite, respectively.

[k] Adjusted for age, sex, education, family history of gastric cancer, combined food score index, intake of β-carotene, vitamin C, and total calories, nitrate, and nitrite.

[l] Adjusted for age, sex, occupation, total calorie intake.

nitrate was reversed to a nonsignificant positive association (OR=1.63, 95% CI = 0.904–3.04) when vitamin C intake was taken into account (both calculated from the consumption of 21 vegetables).

In a study carried out in selected areas of four regions in Spain, including 354 cases of gastric adenocarcinoma and 354 hospital controls matched by age, sex, and area of residence,[16] González et al. concluded that the observed reduced risk for nitrates (adjusted for total calories) might just be an indicator of vegetable consumption, known to be associated with a reduced risk of stomach cancer.[3]

Of the six case-control studies that estimated nitrite intake, five[10–14,16] showed no significant association with stomach cancer risk. In the aforementioned study of Risch et al.,[15] a direct association was observed (OR=2.61, 95% CI=1.61–4.22, adjusted for dietary fiber, chocolate, carbohydrates, no refrigeration, total food consumption, and ethnicity). The same held true for the data of La Vecchia et al.[17,18] in which the interaction between methionine and nitrites was considered. Compared with subjects with low methionine (< 1.5 mg/day) and low nitrite intake (<2.7 mg/day), the OR was 2.45 (95% CI=1.9–3.2) in the high methionine (>1.9 mg/day) and high nitrite (≥2.7 mg/day) stratum. Measures of methionine and nitrite intake were derived from a selected number of foods only. These data were derived from an ongoing case-control study conducted in the Greater Milan area between 1985 and 1993.[17,18]

Of the four studies that estimated NOC intake,[13,15–17] three showed a statistically increased risk with high intake of N-nitrosodimethylamine (NDMA).[13,16,17] In the case-control study conducted by Pobel et al. in Marseilles, France[13], the OR for the third versus the first tertile of intake was 7.00 (95% CI=1.85–26.46, adjusted for age, sex, occupation, and total calorie intake). The wide confidence intervals probably reflect the small number of cases (*n*=92) and give an imprecise estimation of the OR. Only dietary exposure to NDMA was assessed, although it may not be

representative of the whole group of preformed nitrosamines in food. In the study by González et al.,[16] it was suggested that high consumption of a protective factor, such as vitamin C, neutralizes the increased risk observed with consumption of preformed nitrosamines (OR=2.09 in the highest quartile, adjusted for total calories). In the study by La Vecchia et al.,[17] the multivariate OR for the highest NDMA intake tertile was 1.37 (95% CI=1.1–1.7) including age, sex, education, family history of gastric cancer, combined food score index, intake of β-carotene, vitamin C, total calories, nitrite, and nitrate. No information on *H. pylori* in cases and controls was available, although *H. pylori* antibody prevalence has not been shown to correspond to high-risk areas of gastric cancer in Italy.

Table 2[19–22] shows the results of four case-control studies of foods rich in nitrate, nitrite, and N-nitroso compounds and risk of stomach cancer. In 1985, Correa et al.[19] presented results of 391 stomach cancer cases and an equal number of hospital controls with a wide variety of clinical conditions matched by race, sex, and age, with both groups being inhabitants of southern Louisiana. Smoked foods (OR 1.70, 95% CI=1.01–2.87) and homemade sausages or home-cured meats (OR 2.32, 95% CI=1.10–4.87) were associated with a statistically significant increased risk for stomach cancer in blacks but not whites after adjustment for sex, respondent status, income, and duration of smoking. Multiple comparisons made while examining factors related to stomach cancer increased the probability of a statistically significant result owing to chance alone.

A case-control study of 564 stomach cancer patients and 1131 population-based controls was conducted to evaluate reasons for the high rates of stomach cancer in Linqu, in northeast China.[20] Risk of stomach cancer was increased by 50% among families with "moldy grain" supplies (several species of fungus can reduce nitrate to nitrite[23]). These results, however, were adjusted only for sex, age, and income.

Boeing et al.[21] investigated 143 cases of stomach cancer in a high-risk area and a low-risk area for stomach cancer in Germany and compared them with 579 controls who were patients or visitors from the same hospitals matched for age and sex. They reported a nonsignificant negative association with nitrate from food items in a univariate analysis, but this association changed to a nonsignificant positive association in multivariate analysis. Furthermore, the authors reported a significantly elevated risk for users of well water compared with those who used central water supplies at some time during the lifecycle (OR=2.26, 95% CI=1.19–4.28). These results were adjusted only for home meat smoking, years of refrigerator use, age, sex, and hospital. No data were available on water constituents, but analyses from other countries have shown that private water sources can contain considerable amounts of nitrate.

Conversely, Rademacher et al.[22] found no association with nitrate levels in water (central or private water sources) and cancer risk. This large study compared 1268 stomach cancer deaths in Wisconsin residents with an equal number of deaths from other causes matched by sex, year of birth, year of death, Wisconsin birth, and Wisconsin residency at the time of death. There were some weaknesses inherent in the study. The results were not adjusted for other potential confounders, such as ethnicity and dietary habits. Moreover, the place of residence listed on the death certificate (hospitals or nursing homes excluded) was assumed to be the source of the subjects' nitrate exposure

**Table 2.** Case-Control Studies on Foods Rich in Nitrates, Nitrites, or N-Nitroso Compounds and Risk of Stomach Cancer

| Reference and Number of Cases | Dietary Variable | Comparison | Association | Odds Ratio (95% CI) | Population |
|---|---|---|---|---|---|
| Correa et al.[19] (*n*=391) | Smoked foods | Above median intake | ↑ | 1.70 (1.01–2.87)[a] | Louisiana |
| | Homemade sausage or cured meats | Vs. lower intake | ↑ | 2.32 (1.10–4.87)[a] | |
| You et al.[20] (*n*=564) | "Sour pancakes" | Daily vs. <daily | NS | 1.3 (1.0–1.6)[b] | Shandong, China |
| | Moldy grain | Yes vs. never | ↑ | 1.5 (1.2–2.0)[b] | |
| Boeing et al.[21] (*n*=143) | Well and central water | Vs. central water only | ↑ | 2.17 (1.38–3.39)[c] | Germany |
| | Well water | | ↑ | 2.26 (1.19–4.28)[c] | |
| | Nitrate from food items | Quintile 5 vs. quintile 1 | NS | 1.26 (0.59–2.70)[d] | |
| Rademacher et al.[22] (*n*=1268) | Private well | Vs. public water | NS | 1.09 (0.82–1.47)[e] | Wisconsin |
| | >10.0mg/L NO3-N in public sources | Vs. less, or private | NS | 1.50 (0.12–18.25)[e] | |

Note: CI=confidence intervals. NS=statistically not significant. ↑=Statistically significant direct association.

[a] For blacks after adjustment for sex, respondent status, income, duration of smoking.

[b] Adjusted for sex, age, family income.

[c] Adjusted for smoking of meat at home, years of refrigerator, age, sex, hospital.

[d] Adjusted for vitamin C, carotene, calcium, age, sex, hospital.

[e] Crude odds ratio.

via drinking water for at least 20 years before death (the latent period of most carcinogenic exposures). It was concluded that random misclassification error, a major problem in retrospective studies in which past exposure must be estimated, could have existed. Exposure misclassification of this type would tend to bias the OR toward unity.

In general, N-nitroso compounds, found in cured meats, salted foods, etc., may be related to the risk of stomach cancer, but the available epidemiologic evidence is insufficient[8] to confirm this hypothesis.

## Brain Tumors

The most common types of brain tumors are astrocytoma, medulloblastoma, ependymoma, glioblastoma, and meningioma. The age curve of these tumors shows a peak during the first decade of life followed by peaks in adults, except for medulloblastoma, which is rarely observed in adults, and meningioma, which is less prevalent in children than in adults. Brain tumors account for about one in five childhood cancers. Increased incidence has been noted in many countries, mainly in adults, and this may reflect diagnostic improvement. Very little is known about the etiology of brain tumors. One postulated risk factor that has been the subject of investigation is exposure to NOC and precursor nitrates and nitrites, some of which are nervous system carcinogens in animals, especially when exposure occurs transplacentally.[9,24,25]

Table 3[24–30] shows the results of studies of NOC and brain tumors. Five case-control studies[24–28] investigated maternal dietary exposure to nitrosamines during pregnancy. One study considered dietary intakes by children.[27] Two studies investigated all childhood brain tumors combined,[26,27] despite the fact that different brain tumors may have different etiologies.

In Los Angeles County, Preston-Martin et al.[26] questioned mothers of 209 young brain tumor patients and mothers of 209 population-based controls (matched by sex, race, and birth year) about experiences of possible etiologic relevance that they had during pregnancy, including frequency of consumption of cured meats. Results suggested an etiologic role for cured meats (ORs=1.2 for moderate, 2.3 for high versus low, intake; $p$ trend=0.008) and other NOC-containing substances in childhood brain tumors.

In a small Canadian case-control study[27] that compared children's consumption of cured meats before diagnosis (>1 serving/week versus ≤1) in 74 cases and 138 age- and sex-matched population controls, no association was observed.

Newer studies have concentrated on a single type of brain tumor in children. Gestational and familial risk factors were investigated for their association with astrocytoma in a case-control study of 163 pairs (matched by age, race, and telephone exchange) that was performed in Pennsylvania, New Jersey, and Delaware.[25] The researchers observed a significant trend showing more frequent consumption of cured meats in mothers of astrocytoma patients compared with control mothers. However, the association was present only among more highly educated mothers (OR=6.8, 95% CI=1.8–26.3).

Conversely, a study by Bunin et al.[24] showed no elevated risk with frequent maternal consumption of cured meats (quartile 4 versus quartile 1) and primitive neuroectodermal tumor in children. The 166 case patients had a primitive neuroectodermal tumor in the brain diagnosed before the age of 6 years between 1986 and 1989 and were registered with the Children's Cancer Group in North America. The 166 controls (matched by age and race) were selected by random-digit telephone dialing. A parallel study of astrocytic glioma in children (155 case-control pairs) was conducted by the same investigators and interviewers using the identical questionnaire.[28] No significant association between cured meat consumption during pregnancy and risk of astrocytic glioma (adjusted for income level) was shown. Misclassification owing to difficulty in reporting diet during a pregnancy up to 6 years in the past might have contributed to the negative results.

Two investigations concentrated on brain tumors in adults (Table 3). Burch et al.[29] studied 215 adult males (25–80 years of age) diagnosed in southern Ontario between 1979 and 1982 and an equal number of hospital-based controls matched by sex, area of residence, marital status, year of birth, date of diagnosis, and date of death. The study included many dead cases. Thus, the quality of dietary data was poor because of the large number of proxy respondents. The investigators observed elevated risks for reported consumption of spring water (OR=4.33, 95% CI=1.24–15.2) and wine (OR=2.14, 95% CI=1.28–3.60) (ever versus never) for brain tumors in general. Although spring water and wine consumption are consistent with a role for NOC in the etiology of brain tumors, for several other factors related to this hypothesis (e.g., consumption of various processed meat and fish products), no association was observed.

Preston-Martin et al.[30] investigated employment histories and other suspected risk factors of 272 men ages 25–69 with a primary brain tumor first diagnosed during 1980–1984 in Los Angeles County and of 272 age- and race-matched neighbor controls. Separate analyses were conducted for 202 glioma pairs and 70 meningioma pairs. No significant direct association between NOC-rich beer, wine, and hard liquor consumption (ever consumed at least once a month versus less) and risk of gliomas or meningiomas in males was observed.

In summary, although some studies point to weak associations, the available data provide little support for the hypothesis that N-nitroso compounds are involved in the etiology of brain tumors.

Case-Control Studies on Dietary Intake of Nitrates, Nitrites, and N-Nitroso Compounds (or the Corresponding Foods) and the Risk of

| e and er of Cases | Brain Tumor | Dietary Variable | Comparison | Association | Odds Ratio (95%CI) | Population |
|---|---|---|---|---|---|---|
| Martin et al.[26] | "Brain tumors" | Intake during pregnancy | | | | Los Angeles Coun |
| ) | | Cured meats | High vs. lower | ↑ | 2.3[a]; *p* trend=0.008 | children < 25 yea |
| al.[27] | "Brain tumors" | Cured meats (child) | >1×/week vs.≤1 | NS | 1.13 (0.551–2.31)[b] | Southern Ontario |
| | | Beer (pregnancy) | Ever vs. never | ↑ | 3.53 (1.16–10.8)[b] | cases ≤ 19 years |
| t al.[25] | Astrocytoma | Intake during pregnancy | Yes vs. no | NS | 1.9 (0.9–4.2)[a] | Cases < 15 years, |
| ) | | Cured meat | Frequency | ↑ | *p* trend=0.04 | New Jersey, Dela |
| | | Highly educated mothers | High | ↑ | 6.8 (1.8–26.3)[a] | Pennsylvania |
| | | Less educated mothers | High | NS | 1.2 (0.4–3.8)[a] | |
| al.[24] | Primitive neuro- | Intake during pregnancy | | | | U.S., Canadian |
| ) | ectodermal tumor | Nitrate | Quartile 4 vs. | NS | 0.54 (-)[c] | children < 6 year |
| | | Nitrite | quartile 1 | NS | 1.06 (-)[c] | |
| | | Nitrosamines | | NS | 1.55 (-)[c] | |
| | | Cured meat | | NS | 1.10 (0.60–2.03)[a] | |
| al.[28] | Astrocytic glioma | Intake during pregnancy | | | | U.S., Canadian |
| ) | | Cured meats | Quartile 4 vs. | NS | 1.7 (0.8–3.4)[d] | children < 6 year |
| | | Nitrite | quartile 1 | NS | 1.3 (0.7–2.6)[d] | |
| | | Nitrate | | NS | 0.7 (0.3–1.4)[d] | |
| | | Dimethylnitrosamine | | NS | 0.8 (0.4–1.6)[d] | |
| al.[29] | "Brain tumors" | Spring water | Ever vs. never | ↑ | 4.33 (1.24–15.2)[a] | Southern Ontario |
| ) | | Wine | Ever vs. never | ↑ | 2.14 (1.28–3.60)[a] | adults (25–80 ye |
| Martin et al.[30] | Gliomas (G) | Beer | >1×/month vs. less | NS | G: 0.7 (0.5–1.2)[a] | Los Angeles Coun |
| ) | Meningiomas (M) | | | ↓ | M: 0.4 (0.1–0.9)[a] | men (25–69 years |
| | | Wine | | NS | G: 0.7 (0.5–1.1)[a] | |
| | | | | NS | M: 0.7 (0.3–1.4)[a] | |
| | | Hard liquor | | NS | G: 1.3 (0.8–1.9)[a] | |
| | | | | NS | M: 0.7 (0.3–1.4)[a] | |

confidence intervals. NS=not statistically significant. ↑=statistically significant direct association. ↓=statistically significant inverse association.
lds ratio.
l for age at diagnosis.
l for food components and supplements.
l for income level.

## Esophageal Cancer

The highest incidence rates of esophageal cancer are found in the so-called Asian esophageal cancer belt, which stretches from Russia and Turkey to eastern China. In Europe, the highest rates are found in France. It is more common in males in America and Europe, whereas in the high-risk Asian belt, as the incidence rises the proportional male predominance declines. Correlation studies suggest that the causes might not be the same in all countries. Although alcohol and tobacco may account for as much as 90% of esophageal cancer in some Western populations, these factors appear to play a minor role in areas with the highest incidences, such as inland Asia.[23] No clear explanation is available regarding the etiology of Asian belt esophageal cancer. Various hypotheses have been proposed, including diets low in fruits and vegetables, diets inadequate in numerous vitamins and minerals, physical trauma to the esophagus (e.g., by the high temperature of ingested food and beverages), consumption of foods rich in N-nitroso compounds, nitrates, or nitrites (e.g., salted and pickled vegetables), and consumption of moldy foods.[8,9,23,31,32]

Correspondingly, several ecologic studies in China have shown an association between indices of exposure to N-nitroso compounds or precursors (e.g., consumption of pickled vegetables) and esophageal cancer mortality.[32] However, a large-scale case-control study in the high-risk area of Linxian of 1244 patients with cancer of the esophagus or gastric cardia and 1314 population-based age- and sex-matched controls did not detect any increase in risk associated with the use of pickled vegetables.[33] The authors of the study suggested that the control group might have included a large proportion of subjects with chronic esophagitis and dysplasia. These may be premalignant lesions and may therefore share risk factors with esophageal cancer.

In a cohort study[34] conducted in the same area, a total of 1162 subjects from the analytic group of 12,693 developed esophageal cancer over the 15-year follow-up period. Results indicated that traditional or suspected risk factors for esophageal cancer, such as smoking and alcohol use, and consumption of pickled vegetables and moldy food were not risk factors for esophageal (including gastric cardia) cancer, but the findings were adjusted only for age and sex.

These results were reiterated in a hospital-based case-control study of Hu et al.[35] that included 196 cases and 392 controls with other (nonneoplastic, nonesophageal) diseases (matched by sex, age, and area of residence) that was carried out in a low-risk area of northeast China. Salt, salt-preserved foods, and pickled vegetables were not associated with an increased risk of esophageal cancer (Table 4[23,31,33–36]). The results were adjusted for alcohol intake, smoking, income, and occupation. Imperfect recollection of diet in the past might have led to random misclassification, and a limited range of exposure to the investigated foods might have decreased the chances to ascertain significant associations.

Conversely, a case-control study conducted by Cheng et al.[36] of 400 Hong Kong Chinese cases and 1598 age- and sex-matched controls (800 hospital and 798 general practice) showed a direct association between pickled vegetable consumption and esophageal cancer risk. In the analysis, consumption of pickled vegetables was divided into six categories: < once/year, < once/month, 1–3 times/month, 1–3 times/week, 4–6 times/week, and daily and more, with the consumption of < once/year being the reference group. The corresponding ORs adjusted for age, level of education, and birthplace were 2.07 (95% CI=0.93–4.60), 1.64 (95% CI=0.84–3.17), 2.35 (95% CI=1.20–4.61), 5.96 (95% CI=2.4–14.77), and 18.10 (95% CI=4.84–67.71). The test for trend was statistically significant. It should be noted, however, that the last two categories of pickled vegetable consumption consisted of only 20 cases and 23 controls and 14 cases and 5 controls, respectively, thus yielding imprecise estimations of the ORs. In a multivariate model including age, consumption of alcohol, smoking, consumption of green leafy vegetables and citrus fruits, preference for hot drinks or soups, place of birth, education, and domestic dining versus eating out during early adult life, the OR of consumption of pickled food daily or more versus < once/year was 13.12 (95% CI=2.57–66.93), i.e., remained statistically significant.

Similar results were reported in the case-control study by Wang et al.[23] that was conducted in two areas of Shanxi (Yangcheng and Linfen), in north central China. The study included 326 cases and 396 population-based controls matched by sex, age, and residence. Esophageal cancer risk tended to increase with increased intake ("sometimes, often" versus "never, rarely") of moldy foods and pickled vegetable juice (high nitrite concentrations[37]). The results (Table 4) were adjusted only for age, gender, and farming/nonfarming occupation, and in Yangcheng the category "sometimes, often" of the consumption of pickled vegetable juice consisted of only seven cases and two controls.

A population-based case-control study (902 cases, 1552 age- and sex-matched controls) by Gao et al.[31] of esophageal cancer in Shanghai found, after adjusting for smoking, alcohol consumption, and other potential confounders (see Table 4), that consumption of preserved vegetables, fermented bean curd (which may be contaminated with mycotoxins), and salty and deep-fried foods was linked to increased risk, but these results were not consistently statistically significant in subgroups.

With regard to drinking water, Yu et al.[34] showed in their retrospective cohort study in Linxian a significant reduction in risk associated with drinking well instead of surface water. The relative risk of 0.83 (95% CI=0.69–0.99)

**Table 4.** Case-Control Studies on Dietary Intake of Foods Rich in Nitrates, Nitrites, or N-Nitroso Compounds and Risk of Esophageal Cancer in the "Asian Belt"

| Reference and Number of Cases | Dietary Variable | Comparison | Association | Odds Ratio (95% CI) | Population |
|---|---|---|---|---|---|
| Li et al.[33] (*n*=1244) | Pickled vegetables | More than 1×/day vs. never in 1970, high risk communes | NS (M)<br>NS (F) | 0.9 (0.6–1.3)[a]<br>1.1 (0.7–1.7)[a] | Linxian, China |
| Wang et al.[23] (*n*=326) | Pickled vegetable juice | Sometimes/often vs. never/rarely | Yangcheng ↑<br>Linfen ↑ | 3.6 (1.1–18.4)[b]<br>11.6 (6.3–21.6)[b] | Shanxi, China<br>Yangcheng: high risk |
| | Moldy foods | Sometimes/often vs. never/rarely | Yangcheng ↑<br>Linfen ↑ | 5.0 (2.6–9.9)[b]<br>6.5 (3.7–11.2)[b] | Linfen: moderate risk |
| Cheng et al.[36] (*n*=400) | Pickled vegetables | Daily or more vs. <1×/year | ↑ | 13.12 (2.57–66.93)[c] | Hong Kong Chinese |
| Yu et al.[34] (retrospective cohort study) (*n*=1162) | Pickled vegetables<br>Regular moldy food use<br>Water use | Regular vs. occasional/never<br>Yes vs. no<br>Well vs. pond or river | NS<br>NS<br>↓ | RR: 1.03 (0.92–1.15)[d]<br>RR: 1.09 (0.95–1.24)[d]<br>RR: 0.83 (0.69–0.99)[d] | Linxian, China |
| Hu et al.[35] (*n*=196) | Pickled cabbage<br>Fermented soy paste | Quartile 4 vs. quartile 1<br>Quartile 4 vs. quartile 1 | NS<br>NS | 0.7 (0.4–1.2)[e]<br>0.7 (0.4–1.3)[e] | Northeast China: low-risk area |
| Gao et al.[31] (*n*=902) | Salty foods | Very salty vs. not salty | NS (M)<br>↑(F) | 2.27 (0.89–5.77)[f]<br>3.81 (1.27–11.50)[f] | Shanghai, China |
| | Cured foods | Frequently vs. never/seldom | NS (M)<br>NS (F) | 1.25 (0.86–1.84)[f]<br>1.33 (0.84–2.13)[f] | |
| | Preserved<br>Salty vegetables | Quartile 4 vs. quartile 1 | NS (M)<br>↑(F) | 1.2 *p* trend=0.23[g]<br>1.7 *p* trend<0.05[g] | |
| | Fermented bean curd | Quartile 3 vs. quartile 1 | ↑(M)<br>↑(F) | 1.4 *p* trend<0.05[g]<br>1.8 *p* trend<0.01[g] | |
| | Vegetable moldy, dried | Quartile 3 vs. quartile 1 | NS (M)<br>↑(F) | 1.2 *p* trend=0.26[g]<br>1.9 *p* trend<0.01[g] | |

Note: CI=confidence interval. M=male. F=female. NS=statistically not significant. ↑=statistically significant direct association. ↓=statistically significant inverse association. RR=relative risk.

[a] Adjusted for age and (for males) smoking.

[b] Adjusted for age, gender, farm/nonfarm occupation.

[c] Adjusted for age, consumption of alcohol, smoking, consumption of green leafy vegetables, consumption of citrus fruits, preference for hot drinks or soups, whether had meals at home or eating out during early adult life, place of birth, education.

[d] Adjusted for age and sex.

[e] Adjusted for alcohol intake, smoking, income, and occupation.

[f] Adjusted for age, education, birthplace, tea drinking, cigarette smoking, alcohol drinking (men), consumption of preserved foods, vegetables, and fruit.

[g] Adjusted for age, education, birthplace, tea drinking, cigarette smoking, alcohol drinking (men).

was adjusted only for sex and age. The elevated risk observed for surface water might have been related to a higher nitrate content in that water, but no data on the nitrate concentrations of the two water sources were given. No association between water source and esophageal cancer risk was observed in the previously mentioned case-control study of Li et al.[33] that was carried out in the same area (results not shown).

The recent review by the American Institute for Cancer Research[8] concluded that ecologic evidence supported by experimental data suggests that exogenous dietary N-nitrosamine exposure and endogenous N-nitrosamine formation possibly increase the risk of esophageal cancer.

## Nasopharyngeal Cancer

Although tumors of the nasopharynx are rare in most countries, they are prevalent in Chinese residents of Southeast Asia, Arabs in North Africa, and Inuit populations of Mongoloid origin in Canada, Greenland, and Alaska. Known and suspected causes are genetic factors, Epstein-Barr virus (EBV), inhaled substances, smoking, and diet, especially Cantonese salted fish.[8,9]

Case-control studies in southern China, Malaysia, and Hong Kong demonstrated an association between the consumption of salted fish, especially during weaning, and the risk of nasopharyngeal cancer.[38–40] The methods and the results of these and other studies are described in Table 5.[38–45] Ning et al.[41] reported on a case-control study performed in a low-risk region of China (Tianjin) with data from 100 cases of nasopharyngeal cancer and 300 neighborhood controls (matched by age, sex, and race). Exposure to salted fish (ever versus never) was significantly associated with an increased risk of nasopharygeal cancer (OR=2.2, 95% CI=1.3–3.7). The following characteristics of exposure to salted fish independently contributed to the increased risk: earlier age at first exposure, increasing duration and frequency of consumption, and steaming of fish rather than frying, grilling, or boiling it. Results were not adjusted for other risk factors. In a separate analysis, a significant increased risk was observed for the consumption of salted shrimp paste and salted fish when adjusted for each other and for carrot consumption, but not for infection with Epstein-Barr virus and other factors.[41]

A more recent case-control study of Zheng et al.[42] (88 nasopharyngeal cancer cases, 176 age-, sex-, and neighborhood-matched controls) was conducted in Znagwu County, Guangxi, China, and was part of the study of Hubert et al.[46] This multivariate analysis (including the use of wood fuel, consumption of herbal tea, and a sociodemographic score) found a significantly increased risk (OR=3.8, 95% CI=1.5–9.8) for the consumption of salted fish in rice porridge before the age of 2 years. Because subjects provided data on their diet from almost 30 years previously these results may be affected by recall bias.

Additionally, Sriamporn et al.[43] conducted a case-control study with data from 120 nasopharyngeal cancer cases and the same number of hospital-, age-, and sex-matched controls in northeast Thailand, a region that shows an intermediate risk for this neoplasm. The consumption of sea-salted fish at least once a week versus never in adult life was a significant risk factor for nasopharyngeal cancer (OR=2.5, 95% CI=1.2–5.2, adjusted for alcohol, cigarette consumption, occupation, education, and area of residence). Again, EBV infection as a potential confounder was not assessed.

In the recent review by the American Institute for Cancer Research,[8] the overall evidence that diets high in Cantonese-style salted fish increase the risk of nasopharyngeal cancer is considered convincing. Salted fish has a high level of secondary amines. These amines are believed to interact with nitrite salts used as preservatives and lead to the formation of N-nitroso compounds, which are possibly organotrophic for the nasopharynx.[9] This has been demonstrated in vivo by Yu et al.,[47] who induced malignant nasal cavity tumors in rats fed salted fish.

Rates of nasopharyngeal cancer comparable to those in Southeast Asia have been reported in Inuit populations in Canada, Alaska, and Greenland and in Arabs of North Africa. Cantonese Chinese, Maghrebian Arabs, and Eskimos were compared in anthropologic studies by Hubert et al.[46] It should be noted that the diet of Maghrebian Arabs, for example, is very different from that of Chinese and does not include salted fish. The conclusion of Hubert's study was that traditional preserved food preparations could be the common factors linking these groups. Laboratory analyses of food samples from south China, Macao, Tunisia, and Greenland revealed the presence of volatile nitrosamines.[48] In a third step of the study by Hubert et al.,[46] case-control studies in Tunisia and in China tested the hypotheses based on these data. The results suggested that consumption in early youth of salted and preserved foods other than salted fish, such as fermented fish sauce, salted shrimp paste, moldy bean curd, and two kinds of preserved plums, was also associated with an increased risk of nasopharyngeal cancer.[40,44,45]

## Conclusions

N-Nitroso compounds (NOC) are potent carcinogens in animal studies.[1] Epidemiologic evidence of dietary NOC and precursor nitrates and nitrites as human oncogenic agents remains inconclusive. In assessments of the human health risks of dietary exposure to nitrate, nitrite, and NOC, it is important to recognize that the analysis of the exposure is particularly complex.[13] Many NOC have been detected in foods, but only N-nitrosodimethylamine is well studied. Nitrate, nitrite, and NOC concentrations in food products, in addition, can vary widely for the same food or for drinking water from different sites. The accurate

**Table 5.** Case-Control Studies of Foods Rich in Nitrates, Nitrites, or N-Nitroso Compounds and Risk of Nasopharyngeal Cancer

| Reference and Number of Cases | Dietary Variable | Comparison | Association | Odds Ratio (95% CI) | Population |
|---|---|---|---|---|---|
| Armstrong et al.[38] | Consumption during childhood | | | | |
| ($n$=100) | Salted fish | Daily vs. never | ↑ | 17.4 (2.7–111.1)[a] | Malaysian Chinese |
| Yu et al.[39] ($n$=250) | During weaning | | | | |
| | Salted fish | Ever vs. never | ↑ | 7.5 (3.9–14.8)[a] | Hong Kong |
| | At age 10 years | | | | |
| | Salted fish | ≥ 1×/week vs. rarely | ↑ | 37.7 (14.1–100.4)[a] | |
| Yu et al.[44] ($n$=128) | During pregnancy | | | | |
| | Salted fish | Weekly vs. rarely | ↑ | 3.1 (1.1–8.8)[b] | Yulin Prefecture, China |
| | During weaning | | | | |
| | Salted fish | Yes vs. no | ↑ | 2.6 (1.2–5.6)[b] | |
| | Salted duck eggs | | ↑ | 5.0 (1.2–21.0)[b] | |
| | Salted mustard green | | ↑ | 5.4 (1.2–23.8)[b] | |
| | Chung choi | | ↑ | 2.0 (1.3–3.2)[b] | |
| | Age 1–2 years | | | | |
| | Fermented black bean paste | Weekly vs. rarely | ↑ | 4.6 (1.8–11.4)[b] | |
| | Fermented soy bean paste | | ↑ | 3.6 (1.6–8.1)[b] | |
| | Salted fish, dried fish, salted mustard green | | NS | | |
| | At age 10 years | | | | |
| | Dried fish | | ↑ | 6.4 (1.6–26.8)[b] | |
| | Salted fish, fermented black or soy bean paste, chung choi, salted mustard green | | NS | | |
| Yu et al.[40] ($n$=306) | During pregnancy | | | | |
| | Salted fish | Daily vs. rarely | ↑ | 2.2 (1.1–4.6)[a] | Guangzhou, China |
| | During weaning | | | | |
| | Salted fish | Yes/no | ↑ | 2.1 (1.2–3.6)[a] | |
| | Exposure during ages 1–2 | | | | |
| | Salted fish | Weekly vs. rarely | ↑ | 2.0 (1.1–3.6)[a] | |
| | Fermented fish sauce | | NS | $p$ trend=0.07[a] | |
| | Salted shrimp paste | | NS | $p$ trend=0.06[a] | |
| | Moldy bean curd | | ↑ | $p$ trend=0.02[a] | |
| | Around age 10 years | | | | |
| | Salted fish | Daily vs. rarely | ↑ | 2.1 (1.2–3.6)[a] | |
| | Fermented fish sauce | | NS | $p$ trend=0.86[a] | |
| | Salted shrimp paste | | ↑ | $p$ trend=0.02[a] | |
| | Moldy bean curd | | NS | $p$ trend=0.85[a] | |
| | Kind of preserved plum | | ↑ | $p$ trend=0.01[a] | |
| | 3 years ago | | | | |
| | Salted fish | Daily vs. rarely | NS | 1.8 (0.9–3.6)[a] | |
| Jeannell et al.[45] | Preserves/condiments (child) | | | | |
| ($n$=80) | Stewing mixture | Yes/no | ↑ | 8.6 (1.7–43.5)[c] | Tunisia |
| | Snack of harissa | ≥Once/month vs. <once/month | ↑ | 4.2 (1.1–16.7)[c] | |
| Ning et al.[41] ($n$=100) | Salted fish | Ever vs. never | ↑ | 2.2 (1.3–3.7)[a] | Tianjin, China |
| | Age at first exposure (yr) | | | | |
| | ≥21 | | NS | 1.5 (0.7–3.3)[a] | |
| | 11–20 | | NS | 1.9 (0.9–4.0)[a] | |
| | 1–10 | | ↑ | 2.6 (1.5–4.6)[a] | |
| | Duration of consumption (yr) | | | | |
| | 1–10 | | NS | 1.6 (0.9–3.1)[a] | |
| | 11–20 | | ↑ | 2.8 (1.4–5.4)[a] | |
| | ≥21 | | ↑ | 2.8 (1.4–5.6)[a] | |
| | Frequency of consumption (at age 10 years) | | | | |
| | Yearly | | NS | 1.6 (0.8–3.2)[a] | |
| | Monthly | | ↑ | 3.5 (1.6–7.4)[a] | |
| | Weekly/daily | | ↑ | 6.7 (2.2–20.7)[a] | |
| | Cooking method (at age 10 years) | | | | |
| | Steamed | | ↑ | 4.2 (2.2–8.3)[a] | |
| | Other (frying, grilling, boiling) | | NS | 1.6 (0.8–3.2)[a] | |
| | Salted shrimp paste | Weekly/daily vs. none | ↑ | 3.2 ($p$=0.007)[d] | |
| Sriamporn et al.[43] | Adult consumption | | | | |
| ($n$=120) | Salted fish | ≥1×/week vs. none | ↑ | 2.5 (1.2–5.2)[e] | Northeast Thailand |
| Zheng et al.[42] ($n$=88) | Before age 2 years | | | | |
| | Salted fish in rice porridge | Monthly/weekly vs. rarely | ↑ | 3.8 (1.5–9.8)[f] | Guangxi, China |

Note: CI=confidence interval. NS=statistically not significant. ↑=statistically significant direct association.
[a] Crude values.
[b] Adjusted for subject's sex and age.
[c] Matched logistic analysis adjusted for the living conditions score.
[d] Adjusted for consumption of salted fish and carrot consumption.
[e] Adjusted for alcohol, cigarettes, occupation, education, area of residence.
[f] Adjusted for use of wood fuel, consumption of herbal tea, sociodemographic score.

recall of food is another problem in case-control studies.[3] Cohort studies are less prone to this bias, but no prospective study has been reported. Moreover, endogenous production of NOC and its precursors may be a more important source of exposure than exogenous intake. In addition, where exposure appears to have a small effect, the amount of uncontrollable confounding inherent in analytic epidemiologic studies is about as large as the most plausible effect.[49] Finally, many of the studies discussed in this review did not estimate dietary intake of NOC, nitrates, and nitrites, but used dietary intake of individual foods rich in these substances as a proxy measure. Exposure misclassification may explain some of the negative study results.

In summary, although no firm epidemiologic evidence had been found linking stomach, brain, esophageal, and nasopharyngeal cancers to dietary intake of nitrate, nitrite, and NOC, an association cannot be ruled out. The strongest evidence points to an increased risk of nasopharyngeal and esophageal cancer in subjects exposed to high dietary NOC levels.

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