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High Dietary Iron and Copper and Risk of Colorectal Cancer: A Case-Control Study in Burgundy, France

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Abstract: *Several hypotheses have been proposed for colorectal carcinogenesis, including formation of free radicals. A case-control study compared nutrient intake in 171 colorectal cancer cases versus 309 general population controls, using a detailed face-to-face food history questionnaire. A food composition table enabled us to determine the mean composition of the diet in macro- and micronutrients. Dietary intakes were separately categorized into quartiles by gender. Logistic regression models were adjusted for age, sex, energy, exercise, and body mass index. High energy, copper, iron, and vitamin E intakes were associated with an overall increased risk of colorectal cancer. The odds ratios associated with the fourth quartile of intake were 2.3 (95% confidence interval, 1.3–4.0), 2.4 (1.3–4.6), 2.2 (1.1–4.7), and 1.8 (1.0–3.4) for energy, copper, iron, and vitamin E, respectively. There were no significant associations with dietary fiber, folate, calcium, or antioxidant vitamins other than vitamin E. These findings regarding iron and copper suggest that free radicals play an important role in colorectal carcinogenesis, while the findings regarding vitamin E are so far unexplained.*

Introduction

Although the relationship between diet and colorectal cancer has been extensively studied, the specific micronutrients that could have beneficial or deleterious effects remain to be clarified, especially in order to set up preventive intervention studies. Low folate intake has been quite consistently associated with an increased risk of colorectal tumors (1). Supplemental calcium has been found to be associated with a reduced risk of adenoma recurrence in populations with a suboptimal dietary intake (2), while data regarding dietary calcium are inconsistent (3),(4),(5). Intervention studies have so far mainly been devoted to reduction of adenoma recurrence, and their results cannot be easily extrapolated to cancer prevention. Only one intervention study investigated the relationship between antioxidant vitamin supplements and risk of colorectal cancer (6). Supplemental β-carotene and vitamin E had no significant protective effect towards the risk of colorectal cancer. Several hypotheses had been suggested to explain the role of certain micronutrients. The role of free radicals was strongly suggested by experimental and clinical research (7). Particularly the creation of free radicals through the Fenton reaction has been proposed to explain the association between high dietary iron, or red meat, and colorectal cancer (8). We investigated nutrients potentially related to colorectal cancers, especially pro- and antioxidant nutrients, in a region with a distinctive dietary pattern, Burgundy, France.

Methods

Cases and Controls

A case-control study was set up between 1985 and 1990 in order to investigate risk factors for benign and malignant colorectal tumors. Its general design and results regarding food groups have already been presented (9,10). Briefly, the part of the study that investigated colorectal cancer was designed as follows. Calculations for the minimum necessary number of subjects had been based on the hypothesis that lipids played a role, which was a major hypothesis at the time the study was set up. Considering that in industrialized countries, 50% of the population had a high lipid intake, 110 cases and 220 controls were necessary to demonstrate an odds ratio equal to or over 2.0, with an α error of 0.05, and a β error of 0.10. Cases were residents of the Côte d'Or area, aged 30 to 79 years, 109 males and 62 females, with a histologically proven adenocarcinoma of the large bowel diagnosed for the first time in their lives. They were recruited through all of the gastroenterology and surgery departments in the area, with the help of a well-established registry of digestive cancers for the area. During the recruitment period, 1,167 cases of colorectal cancer had been recorded in the area; thus, the

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study group represented 14.7% of the recorded cases. There were no criteria of selection of cancer cases, other than the age limit of 79 years. Cases were successively recruited according to the planning of dieticians in charge of the interviews and the planning of surgical procedures. The dieticians were also in charge of other interviews at the same time, in particular, those of the control group. There were 43 cases in the right colon (25.1%), 63 cases in the left colon (36.8%), and 65 cases in the rectum (38.0%). This site distribution was similar to that of the whole registry in the same period, that is, 24.2%, 39.8%, and 36.0%, respectively. On diagnosis, 26.9% of the tumors were Dukes stage A, 31.9% were Dukes stage B, 25.2% were Dukes stage C, 13.9% were metastatic, and 6.1% could not be classified. Corresponding values for the whole registry in the same period were comparable, 26.9, 38.0, 19.9, 11.7, and 3.5, respectively. Controls (159 males and 150 females) were Côte-d'Or residents who had been randomly selected from the 1975 census list by the National Institute for Statistics and Economic Studies. The sample had been stratified by age and sex to conform to the theoretical distribution of colorectal cancers in the area. For both cases and controls, exclusion criteria were having familial polyposis coli or hereditary nonpolyposis colorectal cancer, or a previous history of colorectal tumor, inflammatory bowel disease, colectomy, or any other type of cancer. Refusal rates were higher among population controls (46.5%) than among cancer cases (20.1%).

Data

The diet history questionnaire has previously been described (11). It was a 2-h detailed questionnaire about the past year's diet, which followed the pattern of meals throughout the day. A specially trained dietician, who also coded the data, administered the questionnaire at the subjects' homes. All nutritional data were transformed into a mean daily intake of nutrients and alcohol; a food composition table was created by compilation of available food composition tables and additional information from the food industry (12), and a program connected the data to it. Thirty-nine nutrients were studied, including macronutrients, vitamins, fatty acids, and minerals.

Dietary intakes were categorized into quartiles from the distribution in the control group, by gender. Range of intake and cutoffs for quartiles are provided in the Appendix.

Analysis

Analyses were performed using multiple logistic regression and adjusting for age, gender, body mass index, physical activity, and energy intake. Odds ratios (ORs) were calculated using the category of lowest consumption as the reference category. Goodness of fit of the model was verified for each variable. Nutrients were also studied according to cancer site using polytomic logistic regression, the three cancer sites being considered as nominal.

Results

ORs corresponding to the relationship between nutrients and risk of colorectal cancer, adjusted for energy intake, age, gender, exercise, and body mass index, are presented in Table 1. Energy was significantly associated with risk of colorectal cancer, OR for the fourth vs. first quartile (OR_4 = 2.0; 95% confidence interval [CI], 1.1–3.5), and in a similar way with its three components, lipids, proteins, and carbohydrates. There were significant positive associations with iron (OR_4 = 2.3; 95% CI, 1.1–4.7), copper (OR_4 =2.3; 95% CI, 1.2–4.4), and vitamin E (OR_4 =1.9; 95% CI, 1.0–3.4). There was no inverse association between any nutrient and risk of colorectal cancer. In a stepwise model including energy, vitamin E, iron, and copper, the effects of copper (P = 0.005) and of vitamin E (P = 0.005) remained independent, while the effects of energy (P = 0.66) and of iron (P = 0.80) were no longer significant.

When considering cancer sites, energy was mostly associated with risk of left colon cancers and, more specifically, its carbohydrate component. Lipids were nonsignificantly associated with risk of left colon and rectal cancers. No component of energy was significantly associated with right colon cancer. The most consistent finding was observed for copper, which was positively associated with risk for all sites, although statistically significant only for rectal cancer. For the other nutrients, opposite effects were observed. Folic acid intake appeared to be significantly and inversely associated with left colon cancer, whereas it was not significantly associated with the other sites, with an indication of an opposite effect on rectal cancer. Findings were similar with β-carotene, with an inverse association with left colon cancer but an opposite effect regarding rectal cancer. Polyunsaturated fatty acids, linoleic acid, and vitamin E appeared to be only associated with rectal cancer, the same being observed for vitamin B_{12}.

Discussion

The main findings from our study include a deleterious effect of high energy, high copper, high iron, and high vitamin E on risk of colorectal cancer. An association between high energy intake and risk of colorectal cancer has already been described by many authors (13), including ourselves in a previous analysis of this data set (9). In our study, high energy intake, and especially the carbohydrate component, was mostly associated with left colon cancer. These findings are in agreement with the hypothesis that the growth hormone/insulin-like growth factor I axis may be important in the development of colorectal cancer (14–16).

In our study, we observed a strong association between both iron and copper intakes and colorectal cancer, the effect being stronger for copper than for iron in a multivariate model. The relationship between iron and colorectal neoplasms has been largely examined, with a view to explain the increased risk of colorectal cancer associated with red meat intake. A recent review of the literature concludes that a

Table 1. Relative Risk of Colorectal Cancer Associated With Nutrient Intake (Adjusted for Age, Sex, Energy Intake,[a] Body Mass Index, and Physical Activity)

	Odds Ratios (95 % confidence interval)				
Consumption Levels[b] Nutrients	1	2	3	4	*P* (for linear trend)
Total energy	1.0	1.3 (0.7–2.4)	1.8 (1.0–3.1)	2.3[c] (1.3–4.0)	0.002
Alcohol-free energy	1.0	1.4 (0.8–2.5)	1.7 (1.0–3.0)	2.0[d] (1.1–3.5)	0.01
Carbohydrates	1.0	1.3 (0.7–2.4)	1.0 (0.5–2.1)	1.4 (0.6–3.2)	0.63
Proteins	1.0	1.1 (0.6–2.1)	1.4 (0.7–3.0)	1.6 (0.6–3.8)	0.28
Lipids	1.0	0.9 (0.5–1.7)	1.0 (0.5–2.2)	1.3 (0.5–3.2)	0.60
Fiber	1.0	0.6 (0.3–1.1)	0.7 (0.4–1.3)	0.9 (0.5–1.7)	0.98
Alcohol	1.0	1.4 (0.8–2.5)	1.4 (0.8–2.5)	1.1 (0.6–2.0)	0.64
Calcium	1.0	1.3 (0.7–2.3)	1.0 (0.6–1.9)	1.4 (0.8–2.6)	0.38
Iron	1.0	1.5 (0.8–2.8)	2.0[d] (1.1–3.8)	2.2[d] (1.1–4.7)	0.02
Copper	1.0	1.0 (0.6–2.0)	1.5 (0.8–2.8)	2.4[c] (1.3–4.6)	0.002
Zinc	1.0	0.8 (0.4–1.5)	1.1 (0.6–2.0)	1.1 (0.6–2.1)	0.50
Vitamin A	1.0	0.8 (0.4–1.5)	1.5 (0.8–2.7)	1.3 (0.7–2.4)	0.11
β-carotene	1.0	1.4 (0.8–2.4)	2.2[c] (1.3–3.8)	0.8 (0.4–1.5)	0.83
Vitamin C	1.0	0.8 (0.4–1.3)	0.9 (0.5–1.5)	0.8 (0.5–1.5)	0.62
Vitamin D	1.0	1.1 (0.6–1.9)	1.4 (0.8–2.4)	1.1 (0.6–2.0)	0.66
Vitamin E	1.0	1.3 (0.7–2.3)	1.6 (0.9–2.8)	1.8 (1.0–3.4)	0.04
Vitamin B_1	1.0	0.9 (0.5–1.7)	1.1 (0.5–2.2)	1.3 (0.6–2.9)	0.49
Vitamin B_6	1.0	1.5 (0.8–2.7)	1.4 (0.7–2.8)	1.9 (0.9–4.0)	0.13
Vitamin B_{12}	1.0	0.9 (0.5–1.7)	1.1 (0.6–1.9)	1.4 (0.8–2.5)	0.21
Folic acid	1.0	1.4 (0.8–2.4)	1.1 (0.6–2.0)	1.1 (0.6–2.0)	0.96
Cholesterol	1.0	0.8 (0.4–1.5)	1.3 (0.7–2.4)	1.0 (0.5–2.0)	0.57
Saturated fatty acids	1.0	1.2 (0.7–2.2)	1.1 (0.6–2.3)	1.4 (0.6–3.2)	0.50
Polyunsaturated fatty acids	1.0	1.3 (0.7–2.4)	1.5 (0.8–2.8)	1.4 (0.7–2.9)	0.28
Monounsaturated fatty acids	1.0	0.8 (0.4–1.4)	0.8 (0.4–1.6)	1.0 (0.4–2.4)	0.95
Oleic acid	1.0	0.9 (0.5–1.6)	0.8 (0.4–1.6)	1.0 (0.4–2.4)	0.96
Linoleic acid	1.0	1.2 (0.6–2.1)	1.4 (0.7–2.5)	1.3 (0.7–2.5)	0.38
Linolenic acid	1.0	1.0 (0.6–1.8)	1.0 (0.5–1.9)	1.2 (0.6–2.7)	0.60

a: Adjusted for energy except for the total and alcohol-free energy models.
b: Lowest nutrient intake (quartile 1): reference category.
c: $P < 0.01$.
d: $P < 0.05$.

majority of studies are in favor of a positive association between dietary iron and colorectal cancer (17). The hypothesized mechanism is through DNA damage due to free radicals generated by the Fenton reaction (8). Few studies have investigated copper as a potentially related factor to colorectal cancer in epidemiological studies, although a recent review of the literature stated that experimental support for the relevance of oxidative damage due to the mechanisms of metal toxicity and carcinogenicity was particularly strong for both iron and copper (18). Although the relationship between copper and neoplasms has mainly been investigated in copper-deficient diets in experimental models (19), our population can rather be defined as a copper-replete population. While the recommended daily requirement has been set to 0.9 mg/day (20), our lowest intake was 0.8 mg/day, and the cutoff for the 1st quartile of intake was 1.7. Only a proportion of ingested dietary copper and iron is absorbed, so that a large proportion remains available for potential local reactions. Because there are strong interactions between minerals, and because they are often brought by the same foods (21), we must remain careful in interpreting these data. The same mechanism of production of free radicals might be involved in our surprising findings of a potentially deleterious effect of vitamin E and β-carotene. Indeed, although these components are mainly antioxidants, adverse effects, probably due to oxidative damage, have been observed with high doses of β-carotene in human intervention studies (22,23), as well as with vitamin E in experimental studies (24). A simplified experimental model even showed that α-tocopherol can produce oxidative damage to DNA in the presence of copper ions (25). However, an intervention study with vitamin E and β-carotene supplementation has shown no increased risk of colorectal tumors and even a slight nonsignificant decrease in risk in the vitamin E arm (26).

Folic acid has been quite consistently associated with a reduced risk of both adenomas and cancers (27), which was not the case in our study. There was an inverse and significant association with left colon cancer, but an opposite, although not significant, effect on rectal cancer. Few studies have separately investigated risk factors for rectal and for colon cancer, especially regarding folic acid. A large Italian case-control study found a stronger protective effect for the rectum than for

the colon (28). On the other hand, a beneficial effect of folate deficiency has been observed on colorectal carcinogenesis (29), suggesting that folic acid may play a negative role on promoted tissues due to its role in cell multiplication.

For many years, the inverse association between dietary fiber intake and risk of colorectal cancer has been one of the strongest paradigms regarding nutritional prevention of cancer, often confirmed by case-control studies (30). However, findings from cohort studies on colorectal cancer (31–33) and intervention studies on adenoma recurrence (34–36) have been equivocal, and most of them did not support this hypothesis. In this study, we did not find any effect of dietary fiber intake, but our range of intake was low considering the recommended amounts for a protective effect (30). In a previous analysis regarding food groups, we failed to find any protective effects of vegetables, except against left colon cancer, of fruit, or of cereal products, the latter being mostly consumed as refined cereal and associated with an increased risk of colorectal cancer (10).

Methodological limitations of such data must be discussed. Our sample size was relatively small and may have lacked the power to demonstrate an inverse association with certain nutrients such as dietary fiber or folate. For the same reason, site-specific differences must be considered only as an indication of possible true differences in risk, but must be confirmed by further studies. The major limitation of case-control studies come from the retrospective dietary interview, leading to potential inaccuracy in the assessment of food intake. This study was designed with special care regarding the dietary interviews. A pilot study was conducted in order to adapt available dietary questionnaires to our population (11). Our food composition table was also established with special care, avoiding missing data and replacing them by proxies from similar foods (12).

Because of high correlation between nutrients and of the complex biological interactions between micronutrients, attributing an effect to any specific nutrient must always be made with care. However, our data indicate that oxidative stress may be an important etiological factor in colorectal carcinogenesis.

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References

1. Giovannucci E: Epidemiologic studies of folate and colorectal neoplasia: a review. *J Nutr* **132,** 2350S–2355S, 2002.
2. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, et al: Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. *Ann N Y Acad Sci* **889,** 138–145, 1999.
3. Kampman E, Slattery ML, Caan B, and Potter JD: Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). *Cancer Causes Control* **11,** 459–466, 2000.
4. Bergsma-Kadijk JA, van ', V, Kampman E, Burema J: Calcium does not protect against colorectal neoplasia. *Epidemiology* **7,** 590–597, 1996.
5. Martinez ME and Willett WC: Calcium, vitamin D, and colorectal cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev* **7,** 163–168, 1998.
6. Albanes D, Malila N, Taylor PR, Huttunen JK, Virtamo J, et al.: Effects of supplemental α-tocopherol and β-carotene on colorectal cancer: results from a controlled trial (Finland). *Cancer Causes Control* **11,** 197–205, 2000.
7. Saygili EI, Akcay T, Konukoglu D, and Papilla C: Glutathione and glutathione-related enzymes in colorectal cancer patients. *J Toxicol Environ Health A* **66,** 411–415, 2003.
8. Babbs CF: Free radicals and the etiology of colon cancer. *Free Radic Biol Med* **8,** 191–200, 1990.
9. Boutron-Ruault MC, Senesse P, Meance S, Belghiti C, and Faivre J: Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. *Nutr Cancer* **39,** 50–57, 2001.
10. Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, et al.: Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). *Eur J Cancer Prev* **8,** 229–235, 1999.
11. Boutron MC, Faivre J, Milan C, Lorcerie B, and Esteve J: A comparison of two diet history questionnaires that measure usual food intake. *Nutr Cancer* **12,** 83–91, 1989.
12. Lieubray-Bornet, B., Grillet-Cousin, N., Belghiti-Desprat, C., Milan, C., Boutron, M. C., et al.: *Food composition table for the analysis of European multicentric studies. Colon Group of the European Cancer Prevention Organization.* Lyon, France: Oza reproduction, 1995.
13. Howe GR, Aronson KJ, Benito E, Castelleto R, Cornee J, et al.: The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control* **8,** 215–228, 1997.
14. Kaaks R, Lundin E, Rinaldi S, Manjer J, Biessy C, et al.: Prospective study of IGF-I, IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. *Cancer Causes Control* **13,** 307–316, 2002.
15. Nomura AM, Stemmermann GN, Lee J, and Pollak MN: Serum insulin-like growth factor I and subsequent risk of colorectal cancer among Japanese-American men. *Am J Epidemiol* **158,** 424–431, 2003.
16. Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, et al.: A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev* **9,** 345–349, 2000.
17. Nelson RL: Iron and colorectal cancer risk: human studies. *Nutr Rev* **59,** 140–148, 2001.
18. Buzard GS and Kasprzak KS: Possible roles of nitric oxide and redox cell signaling in metal-induced toxicity and carcinogenesis: a review. *J Environ Pathol Toxicol Oncol* **19,** 179–199, 2000.
19. Davis CD and Newman S: Inadequate dietary copper increases tumorigenesis in the Min mouse. *Cancer Lett* **159,** 57–62, 2000.
20. Institute of Medicine: *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. A Report of the Panel of Micronutrients, Subcommittees on Upper Refernce Levels of Nutrients and of Interpretation and Uses of Dietary Reference Intakes and the Standing Committee of the Scientific Evaluation of Dietary Reference Intakes.* Washington, DC: National Academy Press, 2001.
21. Goldhaber SB: Trace element risk assessment: essentiality vs. toxicity. *Regul Toxicol Pharmacol* **38,** 232–242, 2003.
22. The effect of vitamin E and β carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med* **330,** 1029–1035, 1994.

23. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, et al.: Effects of a combination of β carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* **334,** 1150–1155, 1996.
24. Toth B and Patil K: Enhancing effect of vitamin E on murine intestinal tumorigenesis by 1,2-dimethylhydrazine dihydrochloride. *J Natl Cancer Inst* **70,** 1107–1111, 1983.
25. Yamashita N, Murata M, Inoue S, Burkitt MJ, Milne L, et al.: Alpha-tocopherol induces oxidative damage to DNA in the presence of copper(II) ions. *Chem Res Toxicol* **11,** 855–862, 1998.
26. Albanes D, Malila N, Taylor PR, Huttunen JK, Virtamo J, et al.: Effects of supplemental α-tocopherol and β-carotene on colorectal cancer: results from a controlled trial (Finland). *Cancer Causes Control* **11,** 197–205, 2000.
27. Giovannucci E: Epidemiologic studies of folate and colorectal neoplasia: a review. *J Nutr* **132,** 2350S–2355S, 2002.
28. La Vecchia C, Negri E, Pelucchi C, and Franceschi S: Dietary folate and colorectal cancer. *Int J Cancer* **102,** 545–547, 2002.
29. Le Leu RK, Young GP, and McIntosh GH: Folate deficiency reduces the development of colorectal cancer in rats. *Carcinogenesis* **21,** 2261–2265, 2000.
30. Howe GR, Benito E, Castelleto R, Cornee J, Esteve J, et al.: Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* **84,** 1887–1896, 1992.
31. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, et al.: Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med* **340,** 169–176, 1999.
32. Michels KB, Edward G, Joshipura KJ, Rosner BA, Stampfer MJ, et al.: Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* **92,** 1740–1752, 2000.
33. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, et al.: Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* **361,** 1496–1501, 2003.
34. Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, and Faivre J: Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* **356,** 1300–1306, 2000.
35. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, et al.: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* **342,** 1149–1155, 2000.
36. Alberts DS, Martinez ME, Roe DJ, Guillen-Rodriguez JM, Marshall JR, et al.: Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. *N Engl J Med* **342,** 1156–1162, 2000.

Appendix. Range of Intake and Cutoffs for Quartiles of Daily Consumption of Nutrients by Sex

Nutrients	Sex	Cutoffs for Quartiles				
		Lowest Intake	2	3	4	Largest Intake
Energy (kcal)	Male	1024.0	1869.9	2277.2	2789.7	4983.0
	Female	722.6	1443.1	1726.5	2137.5	6362.5
Carbohydrates (g)	Male	85.5	197.7	247.1	304.9	704.8
	Female	50.1	162.2	200.4	229.6	954.4
Proteins (g)	Male	44.6	80.8	96.9	115.9	197.5
	Female	37.1	62.4	71.0	93.1	209.2
Lipids (g)	Male	29.7	80.3	99.0	123.7	270.8
	Female	23.9	60.7	76.5	101.6	213.0
Fiber (g)	Male	5.3	15.2	18.5	22.4	43.0
	Female	6.1	12.7	15.9	18.2	34.3
Alcohol (g)	Male	0.0	15.8	34.4	67.9	320.1
	Female	0.0	0.2	2.0	10.2	76.0
Calcium (mg)	Male	321.1	823.3	998.7	1241.3	3078.0
	Female	365.6	752.3	950.2	1168.6	5008.5
Iron (mg)	Male	5.5	13.3	16.5	21.1	52.5
	Female	4.8	9.0	10.8	12.8	45.1
Copper (mg)	Male	0.8	1.7	2.1	2.7	6.6
	Female	0.8	1.2	1.5	1.8	5.0
Zinc (mg)	Male	5.0	9.9	11.8	14.6	44.4
	Female	4.8	8.3	10.6	15.0	50.9
Vitamin A (μg)	Male	130.6	396.2	678.9	1193.0	5868.6
	Female	44.9	323.2	494.2	972.0	3684.9
β-Carotene (μg)	Male	708.8	3344.8	4476.1	6787.9	14102.0
	Female	1165.9	3230.2	4852.6	6837.0	20527.0
Vitamin C (mg)	Male	12.6	56.6	77.4	104.7	264.6
	Female	18.4	58.8	79.5	107.7	209.3
Vitamin D (μg)	Male	0.6	2.6	3.8	5.3	20.4
	Female	0.7	2.2	2.9	4.3	16.3
Vitamin E (mg)	Male	2.7	8.1	11.8	17.1	46.0
	Female	2.5	6.7	9.7	13.6	30.6
Vitamin B_1 (mg)	Male	0.6	1.1	1.5	1.8	3.4
	Female	0.5	0.9	1.1	1.3	2.4
Vitamin B_6 (mg)	Male	0.6	1.5	1.8	2.2	3.4
	Female	0.7	1.2	1.4	1.7	2.5
Vitamin B_{12} (μg)	Male	2.0	6.7	9.7	13.5	43.4
	Female	2.0	4.8	6.9	9.8	28.7
Folic acid (μg)	Male	79.8	231.6	286.7	350.3	565.8
	Female	116.8	195.2	249.6	300.7	665.7
Cholesterol (mg)	Male	122.9	359.5	449.9	573.1	1127.7
	Female	124.5	273.3	352.4	480.6	1034.6
Saturated fatty acids (g)	Male	8.9	31.9	41.3	50.8	126.7
	Female	7.7	25.0	33.0	44.0	116.5
Polyunsaturated fatty acids (g)	Male	2.6	10.4	13.9	18.8	47.5
	Female	2.1	7.9	10.4	14.4	36.8
Monounsaturated fatty acids (g)	Male	10.0	28.5	35.6	44.5	98.0
	Female	8.1	21.1	28.0	35.6	72.7
Oleic acid (g)	Male	9.2	25.6	32.2	40.3	88.7
	Female	7.3	18.7	25.3	32.1	61.6
Linoleic acid (g)	Male	1.8	9.1	12.2	17.1	45.5
	Female	1.6	6.5	9.0	12.8	34.4
Linolenic acid (g)	Male	0.3	0.8	1.1	1.3	4.7
	Female	0.2	0.6	0.8	1.1	3.0