The Japan Public Health Center (JPHC)–Based Prospective Study was started in 1990 for cohort I and in 1993 for cohort II. Subjects were all registered Japanese residents in 11 public health center areas who were aged 40–69 years at the beginning of the baseline survey. Details of the study design have been described previously (6). The institutional review board of the National Cancer Center, Tokyo, Japan, approved the study. The participants in the present study were subjects in the JPHC study who responded to the 5-year follow-up questionnaire covering lifestyle factors, including food intake, in 1995–1999 at ages 45–74 years. This follow-up survey was used as the starting point in the present study. We did not include one PHC area in the analysis because it had no incidence data and, therefore, we identified 133,323 subjects as the study population. After excluding subjects with non-Japanese nationality ($n = 51$), a late report of emigration occurring before the starting point ($n = 184$), ineligibility due to incorrect birth date ($n = 7$), or duplicate enrollment ($n = 4$), we established a population-based cohort of 133,077 subjects. After exclusion of 12,056 subjects who had died, moved away from the study area, or been lost to follow-up before the starting point, 121,021 subjects were left as eligible. Among them, 98,466 subjects responded to the questionnaire, yielding a response rate of 81.4%.

Questionnaire

We asked subjects to reply to a lifestyle questionnaire that covered sociodemographic characteristics, medical history, smoking and drinking habits, diet, and so on. We designed the

food frequency questionnaire (FFQ) to estimate dietary intake from 138 food items and validated it for the estimation of various nutrients and food groups (7). The FFQ asked subjects about their usual intake of 138 food items during the previous year in standard portions/units and nine frequency categories (never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, once/d, 2–3 times/d, 4–6 times/d, and ≥7 times/d). Nineteen items regarded fish and shellfish, including salted fish, dried fish, canned tuna, salmon or trout, bonito or tuna, cod or flat fish, seabream, horse mackerel or sardine, mackerel pike or mackerel, dried small fish, salted roe, eel, squid, octopus, prawn, short-necked clam or crab shell, vivipara, *chikuwa* (fish paste product), and *kamaboko* (fish paste product). Standard portion sizes for each food item were small (50% smaller), medium (within 50% of the standard), and large (50% larger). We calculated food intake in grams per day by multiplying frequency by standard portion size for each food item. We calculated daily intake of n-3 PUFAs and the specific PUFA, that is, EPA, DHA, DPA, ALA, and n-6 PUFA, using a FA composition table of Japanese foods (8). For some food that was not included in the table, the study used a developed (substituted) FA composition table (9). EPA, DPA, and DHA were summarized as marine n-3 PUFAs.

We assessed validity among subsamples using the 138-item FFQ with 14-day (for one subtropical area) or 28-day (for other areas) weighted dietary records (10). Based on 102 men and 113 women in cohort I, Spearman rank correlation coefficients between each marine n-3

PUFA intake estimated from the FFQ and intake estimated from dietary records were as follows: EPA, 0.38 and 0.45; DPA, 0.32 and 0.39; DHA, 0.34 and 0.37, for energy-adjusted value in men and women, respectively. For ALA, total n-3, and total n-6, the values were 0.27 and 0.25; 0.21 and 0.34; and 0.30 and 0.21, respectively. For the n-6/n-3 ratio, the value for the crude estimate was 0.40 and 0.37 in men and women, respectively.

We excluded subjects who had been diagnosed or reported as having cancer before the starting point (n = 4097), who had missing data regarding FA intake (n = 1182), or who reported extreme total energy intake (upper 2.5% or lower 2.5%). The final analysis included 88,574 subjects (41,382 men and 47,192 women).

Follow-up and identification of CRC cases

We followed subjects from the 5-year follow-up survey (1995–1999) until December 31, 2006; the average follow-up period was 9.3 years. We identified changes in residence status, including survival, annually through the residential registry in each area or, for those who had moved from the area, through the municipal office of the area to which they had moved. Mortality data for persons in the residential registry are forwarded to the Ministry of Health, Labor, and Welfare and are coded for inclusion in the national Vital Statistics database. Residency registration and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are thought to be complete. During the follow-up period in the present study, 8040 (9.1%) subjects died, 4167 (4.7%)

moved away from the study area, and 264 (0.3%) were lost to follow-up.

We identified incident data for CRC by active patient notification from major local hospitals in the study area and from data linkage with population-based cancer registries. We coded CRC cases according to the *International Classification of Diseases for Oncology*, 3rd edition (11) (C18–C20). We conducted analyses of site-specific cancers: C18 for colon cancer (C18.0–C18.5 for proximal colon cancer and C18.6–C18.7 for distal colon cancer) and C19 and C20 for rectal cancer. According to the depth of tumor invasion, invasive cases were defined by cancer over a mucosal layer. In our cancer registry system, the proportion of cases for which information was available from death certificates only was 2.5% for CRC.

Statistical analysis

We calculated person-years of follow-up for each subject from the starting point to the date of cancer diagnosis, date of emigration from the study area, date of death, or end of the follow-up (December 31, 2006), whichever came first. We censored subjects lost to follow-up at the last confirmed date of presence in the study area. The present analysis accrued a total of 380,682 and 447,151 person-years for men and women, respectively.

We calculated relative risks (RRs) and 95% confidence intervals (CIs) of developing CRC for the categories of energy-adjusted FA consumption in quintiles for men and women separately, with the lowest consumption category as the reference. A residual model was used for energy adjustment (12). We used Cox proportional hazards models with adjustment for

potential confounding variables such as age in years (<49, 50–54, 55–59, 60–64, 65–69, and >70); PHC area; body mass index (BMI; <24.9, 25–26.9, 27–29.9, and >30); smoking status (never, past, and current); alcohol drinking in grams of ethanol per week (none, occasional, 1–149, 150–299, 300–449, and ≥450 g/wk); diabetes mellitus (DM; medication use or history); physical activity in metabolic equivalent task (MET)-hours per day (quartile); screening examinations (fecal occult blood test, barium enema, or colonoscopy) for CRC; and quintiles of total calorie, energy-adjusted intake of calcium, vitamin D, fiber, and red meat. The effects of the interaction of each FA and selected environmental factors such as calcium, fiber, and vitamin D were also assessed by adding a multiplicative interaction term to the model. We calculated trend *P* by assigning a median value in each category. All *P* values are two-sided, and statistical significance was determined at the $P < 0.05$ level. We performed all statistical analyses with SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

During 827,833 person-years of follow-up, we identified 1268 new CRC cases (521 colon and 253 rectal for men; 350 colon and 144 rectal for women). Proximal and distal colon cancer developed in 213 and 281 men and 204 and 125 women, respectively.

Table 1 shows the baseline characteristics of the study subjects according to quintile of marine n-3 PUFA, total n-3 PUFA, and total n-6 PUFA in men and women (only the first,

152 third, and fifth quintiles are listed). Men and women with a high intake of these PUFAs were
153 more likely to be old; to have a history of or current use of medications for DM; to have
154 undergone CRC screening; and to have a higher intake of vitamin D, fiber, fish, vegetables,
155 dressing, cooking oil, fats, and other oils. In general, the proportions of overweight subjects
156 and red meat intake were higher among those with high total n-3 PUFA or n-6 PUFA intake or
157 low marine n-3 PUFA intake. Current smoking was less frequent among those with a high
158 intake of these PUFAs, except marine PUFAs in men. Calcium intake was distributed
159 differently between men and women. A U-shaped distribution was seen for total energy intake
160 among those with marine n-3 PUFA and total n-3 PUFA intakes.

161 Associations of marine n-3 PUFAs, ALA, and total n-3 and n-6 PUFAs, and their
162 ratios and risk of colon and rectal cancer in men and women are shown separately (Tables 2
163 and 3). In men, no association was found between these PUFAs and colon cancer overall
164 (Table 2). When cancers were restricted to invasive tumors, similar results were found (data
165 not shown). However, when cases were subdivided by tumor location, we observed
166 statistically significant risk reduction for EPA, DPA, and marine PUFA and proximal colon
167 cancer; *P* values for trend were 0.008, 0.02, and 0.047, respectively. Although not statistically
168 significant, the RR tended to decrease with ALA intake, and finally, total n-3 PUFA was
169 statistically significantly associated with a reduced risk of proximal colon cancer. Compared
170 to the lowest quintile, the RRs (95% CIs) of the second, third, fourth, and fifth quintiles of

171 total n-3 PUFA intake were 0.75 (0.43-1.32), 0.56 (0.29-1.08), 0.46 (0.22-0.97), and 0.42
172 (0.18-0.98), respectively (*P* for trend = 0.0496). Also, we observed reduced risk for n-6 PUFA
173 intake (*P* for trend = 0.04). In contrast, no association was observed between these PUFAs and
174 distal colon cancer. For rectal cancer, we observed the lowest RR for the third quintile across
175 all n-3 PUFAs, which was statistically significant for EPA, 0.51 (0.28–0.92), and marine
176 PUFA, 0.51 (0.27–0.95), respectively. A higher level of intake of these PUFAs did not further
177 reduce the risk of rectal cancer. We observed no apparent association for total n-6 PUFA and
178 the n-3/n-6 ratio.

179 For women, we observed a statistically significant reduced risk among marine n-3
180 PUFAs and each specific marine n-3 PUFA and colon cancer (Table 3). Compared to the
181 lowest quintile, the RR was about half for EPA, DHA, and DPA. We obtained similar results
182 for invasive colon cancer. Similar to men, the inverse associations for marine n-3 PUFAs and
183 their specific PUFA were more prominent in proximal colon compared to distal colon,
184 whereas some of the trend failed to reach statistical significance; for proximal colon cancer, *P*
185 values for trend of EPA, DHA, DPA, and marine n-3 PUFA were 0.07, 0.13, 0.02, and 0.19,
186 respectively. These trends became statistically significant when all colon cancers were
187 combined. ALA showed no association with colon cancer, and finally, for total n-3 PUFAs,
188 although a reduced risk was suggested by increased intake, it failed to reach statistical
189 significance (*P* = 0.15). For rectal cancer, we observed the lowest RR for the second quintile

across all n-3 marine PUFAs, but this was not statistically significant. We observed neither association for total n-3 PUFA and rectal cancer nor for total n-6 PUFA, the n-3/n-6 ratio, and colon and rectal cancer.

Further analyses to check the effect of stratification by smoking status and interaction with selected factors such as calcium, fiber, and vitamin D intakes were conducted. When subjects were limited to those who had never smoked, the RR was generally attenuated; for example, the RR and 95% CI of the highest quintile of marine n-3 PUFAs for developing rectal cancer among men became 0.79 and 0.16–3.87. However, the results are based on a relatively small sample size (61 rectal cancers), and these subjects were kept in the analysis, as shown in Table 2. Among potential factors, we selected *a priori* calcium and fiber as luminal modifiers, based on findings from a recent large case-control study including more than 1000 CRC cases (13) and vitamin D based on our previous report on the risk of CRC (14). For men, an interaction was suggested between calcium and n-3 PUFAs, and vitamin D and some types of marine n-3 PUFAs (EPA and DPA) among rectal cancer cases. For women, an interaction was suggested between calcium and ALA among rectal cancer cases and vitamin D and n-3 PUFAs among colon cancer cases. However, adding interaction terms to the model essentially did not alter the results.

Discussion

In this large, population-based prospective study, which is characterized by high fish consumption and a wide range of n-3 PUFA intakes, marine n-3 PUFAs and specific PUFAs were inversely related to the risk of colon cancer in the proximal site in men. A similar trend was observed in women and it became statistically significant when total colon cancers were combined.

Environmental factors that could favor the development of proximal or distal colon tumors include diet, physical activity, smoking, cholecystectomy, and so on (15). Fermentation reactions leading to short-chain FA production are up to 8-fold higher in the proximal compared to the distal colon (16). On the other hand, levels of the promutagenic lesion O^6-methyldeoxyguanosine, a marker of exposure to N-nitroso compounds, are higher in the normal distal compared to the proximal colonic DNA of patients with CRC (17). Therefore, it is possible that the main effects of PUFAs are more strongly related to the proximal than the distal parts of the large bowel, and a harmful effect, if any, is likely to appear in the distal site. To date, six cohort studies have investigated the relationship between marine n-3 PUFAs and CRC risk, and two studies showed a decreased risk by analyzing marine n-3 PUFA intake (18) or serum levels of DPA and DHA (19), but not all (5, 20–22). Among them, only two studies (5, 18) demonstrated the results separately for the colon and rectum, which showed similar results by site. No study separated the colon by proximal or distal regions. This is the first prospective study to show the different results by subsite.

In contrast with the linear trend shown in marine n-3 PUFAs and colon cancer, the dose response was not clear; rather, we observed a U-shaped association for rectal cancer in men and women. As mentioned earlier, some harmful effect, if any, may be apt to appear in the distal part of the large intestine. Several causes of such effects include cigarette smoking, chemical contaminants in fish, presence of DM, and heterocyclic aromatic amines. Recently, CRC has been included among tobacco-related cancers by the International Agency for Research on Cancer (23). Interestingly, the association is known to be more pronounced in rectal cancer. As stated earlier, the results were generally attenuated when subjects were limited to those who had never smoked, which suggest that smoking might explain, to some extent, the present findings. Nevertheless, when we calculated the RR with adjustment for cigarette smoking, the effect of residual confounding may still exist. However, considering the number of cigarettes per day (<20 or ≥20) for current smokers and lifetime smoking (pack-years) for ever smokers in the adjustment for smoking status did not alter the results from the original ones. Furthermore, treating age, BMI, physical activity (METs-hour) as well as nutrient data as continuous variables also did not alter the results. According to a recent report based on both separate and combined analyses of three large cohort studies in the United States, the Nurses' Health Study, the Nurses' Health Study 2, and the Health Professionals Follow-Up Study, higher intake of long-chain n-3 PUFAs and fish increases the risk of type 2 DM (24). Long-chain n-3 PUFAs can lower glucose utilization, and the authors

247 suggest that increased circulating concentrations of glucose or interruption of
248 insulin-signaling pathways by toxins, such as dioxins and methyl mercury, may contribute to
249 the association. DM is a known risk factor for CRC, and it is possible that some harmful
250 effects may exist through this mechanism. Furthermore, it is also possible that heterocyclic
251 amines, formed as a byproduct of reactions during the cooking of fish at high temperatures,
252 have posed a potential risk for development of CRC (25–27). A review based on a large body
253 of literature spanning numerous cohorts from many countries and with different demographic
254 characteristics did not provide evidence to suggest a significant association between n-3 FAs
255 and cancer incidence (28). Our significant findings among colon cancers may be largely due
256 to the wide range of fish intake in our population.

257 Regarding n-6 PUFAs, we generally observed no association but rather an inverse
258 association for the proximal colon in men. This is in line with previous studies (29), but not all.
259 In a meta-analysis of LA, main n-6 PUFAs, and CRC risk, based on 11 case-control studies,
260 the pooled odds ratio per 21.3 g LA intake was calculated as 0.92 (0.85–1.08) for all subjects,
261 1.05 (0.90–1.23) for men, and 0.80 (0.66–0.98) for women (29). Similarly, based on four
262 cohort studies, the combined RR with high compared to low intakes of LA was calculated as
263 0.92 (0.70–1.22). On the other hand, significant or non-significant increased risks posed by
264 n-6 PUFAs were observed in studies not only for CRC (20, 22) but also for breast cancer in
265 specific situations (30, 31). Several reasons are plausible to explain the discrepancies among

266 studies. Dietary sources of n-3 and n-6 PUFAs include several common foods and, therefore,
267 the effects of n-6 PUFAs may be masked by those of n-3 PUFAs. Actually, on the basis of our
268 previous investigation, the top food in cumulative percentage contribution for n-3 and n-6
269 PUFAs assessed by the dietary record was "vegetable oils/vegetable oil, mixed," which
270 contributed 25.2% and 35.2% of n-3 and n-6 PUFAs, respectively (10). Therefore, when
271 further adjusted for ALA or n-3 PUFA intake, the association in the proximal colon among
272 men was attenuated, and the trend was no longer significant (data not shown). In addition to
273 cooking oil, n-6 PUFAs were contributed by many kinds of lean foods traditionally consumed
274 among Japanese such as rice, tofu (soybean curd), and miso. This is in contrast with the
275 contributors of n-6 PUFAs reported in the U.S. cohort: salad dressing, peanut butter, and
276 margarine (20). By means of observational study, it is actually difficult to completely
277 eliminate the effects of other nutrients included in these foods. Furthermore, because these
278 foods are consumed on a daily basis and might have small between-person variabilities, the
279 association, if any, might have been attenuated. Because of the marginally decreased risk of
280 CRC for n-3 PUFAs and no association for n-6 PUFAs, the ratio also did not indicate any
281 association.

282 This study has several possible limitations. First, we could not adjust for the effect of
283 use of nonsteroidal anti-inflammatory drugs, which may act as anti-inflammatory agents
284 through common pathways to n-3 PUFAs. However, considering the various mechanisms

involved in PUFA intake and CRC risk, the extent of this influence might not be so large. Second, although the validity of PUFA intakes was reasonably high for each marine n-3 PUFA, the validities of ALA, total n-3 PUFAs, and total n-6 PUFA intakes were relatively low. This may be due to the difficulty of assessing "vegetable oils," which are the main common source of these PUFAs. Therefore, caution is needed in interpreting results for these PUFAs. Third, because we conducted multiple comparisons in the analyses, including the differences between colon and rectum and between proximal and distal colon, an interaction effect, some results may be explained, in part, by chance. However, the observed associations were generally consistent for both men and women and also could be reasonably explained by the previously mentioned mechanisms.

The advantage of the study was its prospective design, which enabled us to avoid exposure recall bias. We selected subjects from the general population, we kept the sample size large, the response rate for the questionnaire was acceptable for studies of settings like this, and the number of subjects lost to follow-up was negligible. In addition, the cancer registry was of sufficient quality to reduce the misclassification of the outcome. Japanese people consume much more fish than Western individuals and the Japanese diet has a greater variation of n-3 marine PUFA intake. Based on data from 28 countries with diet recalls, weighing records, or FFQ, in comparison with the United States and most of the European countries, the mean daily intake of combined EPA and DHA among adults was about 5 times

and 2-3 times higher in Japan, respectively (32). Furthermore, using random sampling methods in six regions in Japan, serum n-3 PUFA levels varied significantly by region, which corresponded to the differences in fish consumption (33). In a previous report from our study based on the baseline questionnaire, we observed no association for fish, EPA, DHA, and the n-3/n-6 ratio (5). Owing to the greater detail of the FFQ used in the present analysis compared to that used for the previous report, the variation of marine-based n-3 PUFAs became larger; the median of EPA and DHA intake for the highest group in the present study almost doubled that for the previous one, and the validity of n-6 PUFAs was improved enough to conduct the analysis. The substantial growth in number of observed cases (705 to 1268) also allowed us to conduct more informative analysis by subsite of colon (proximal and distal).

In conclusion, our results from a population with high fish consumption and a wide range of n-3 PUFA intakes suggest that PUFAs of marine origin may be inversely related to the risk of cancer in proximal sites of the large bowel.

Appendix

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References

1. Riediger ND, Othman RA, Suh M, Moghadasian MH. A systemic review of the roles of n-3 fatty acids in health and disease. *J Am Diet Assoc* 2009;**109**:668–79.

2. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *Am J Clin Nutr* 2004;**79**:935–45.

3. Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. *Circulation* 2009;**119**:902–7.

4. World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity, and the prevention of cancer: a global perspective.* Washington, DC: American Institute for Cancer Research, 2007. 517p.

5. Kobayashi M, Tsubono Y, Otani T, Hanaoka T, Sobue T, Tsugane S. Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. *Nutr Cancer* 2004;**49**:32–40.

6. Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. Japan Public Health Center–Based Prospective Study on Cancer and Cardiovascular Diseases. *J*

379 *Epidemiol* 2001;**11**(6 Suppl):S24–9.

380 7. Tsubono Y, Takamori S, Kobayashi M, Takahashi T, Iwase Y, Iitoi Y, Akabane M,

381 Yamaguchi M, Tsugane S. A data-based approach for designing a semiquantitative food

382 frequency questionnaire for a population-based prospective study in Japan. *J Epidemiol*

383 1996;**6**:45–53.

384 8. Science and Technology Agency, eds. *Fatty acids, cholesterol, vitamin E composition tables*

385 *of Japanese foods* (in Japanese). Tokyo: Ishiyaku Shuppan, 1990. 182p.

386 9. Sasaki S, Kobayashi M, Tsugane S. Development of substituted fatty acid food composition

387 table for the use in nutritional epidemiologic studies for Japanese populations: its

388 methodological backgrounds and the evaluation. *J Epidemiol* 1999;**9**:190–207.

389 10. Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Tsugane S. Validity of a

390 self-administered food frequency questionnaire used in the 5-year follow-up survey of the

391 JPHC Study Cohort I to assess fatty acid intake: comparison with dietary records and serum

392 phospholipid level. *J Epidemiol* 2003;**13**(1 Suppl):S64–81.

393 11. World Health Organization. *International classification of diseases for oncology,* 3rd ed.

394 Geneva, Switzerland: World Health Organization, 2000. 490p.

395 12. Willett WC. *Nutritional epidemiology,* 2nd ed. New York: Oxford University Press, 1998.

396 514p.

397 13. Kato I, Majumdar AP, Land SJ, Barnholtz-Sloan JS, Severson RK. Dietary fatty acids,

398 luminal modifiers, and risk of colorectal cancer. *Int J Cancer* 2010;**127**:942–51.

399 14. Ishihara J, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Dietary calcium, vitamin D, and

400 the risk of colorectal cancer. *Am J Clin Nutr* 2008;**88**:1576–83.

401 15. Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer* 2002;**101**:403–8.

402 16. Macfarlane GT, Gibson GR, Cummings JH. Comparison of fermentation reactions in

403 different regions of the human colon. *J Appl Bacteriol* 1992;**72**:57–64.

404 17. Povey AC, Hall CN, Badawi AF, Cooper DP, O'Connor PJ. Elevated levels of the

405 pro-carcinogenic adduct, O(6)-methylguanine, in normal DNA from the cancer prone regions

406 of the large bowel. *Gut* 2000;**47**:362–5.

407 18. Hall MN, Chavarro JE, Lee IM, Willett WC, Ma J. A 22-year prospective study of fish,

408 n-3 fatty acid intake, and colorectal cancer risk in men. *Cancer Epidemiol Biomarkers Prev*

409 2008;**17**:1136–43.

410 19. Kojima M, Wakai K, Tokudome S, Suzuki K, Tamakoshi K, Watanabe Y, Kawado M,

411 Hashimoto S, Hayakawa N, Ozasa K, Toyoshima H, Suzuki S, et al; JACC Study Group.

412 Serum levels of polyunsaturated fatty acids and risk of colorectal cancer: a prospective study.

413 *Am J Epidemiol* 2005;**161**:462–71.

414 20. Daniel CR, McCullough ML, Patel RC, Jacobs EJ, Flanders WD, Thun MJ, Calle EE.

415 Dietary intake of omega-6 and omega-3 fatty acids and risk of colorectal cancer in a

416 prospective cohort of U.S. men and women. *Cancer Epidemiol Biomarkers Prev*

2009;**18**:516–25.

21. Terry P, Bergkvist L, Holmberg L, Wolk A. No association between fat and fatty acids intake and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:913–4.

22. Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, Virtamo J. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 1999;**10**:387–96.

23. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens—part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009;**10**:1033–4.

24. Kaushik M, Mozaffarian D, Spiegelman D, Manson JE, Willett WC, Hu FB. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. *Am J Clin Nutr* 2009;**90**:613–20.

25. Cross AJ, Ferrucci LM, Risch A, Graubard BI, Ward MH, Park Y, Hollenbeck AR, Schatzkin A, Sinha R. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res* 2010;**70**:2406–14.

26. Rohrmann S, Hermann S, Linseisen J. Heterocyclic aromatic amine intake increases colorectal adenoma risk: findings from a prospective European cohort study. *Am J Clin Nutr*