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Epidemiology, Diet and Colorectal Cancer

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THIS presentation is organized into five sections dealing, respectively, with: (i) the descriptive epidemiology of colorectal cancer, (ii) the established or suspected causal factors of probably minor numerical importance, (iii) the epidemiologic evidence implicating diet in the etiology of the majority of cases of large bowel cancer, (iv) the postulated pathogenesis of the diet-related colorectal cancer, and (v) the possible reasons for the frequently unconclusive and occasionally conflicting results of epidemiologic studies exploring the role of diet in the etiology of large bowel cancer. Because of lack of space only a few reviews and selected recent papers will be cited.

DESCRIPTIVE EPIDEMIOLOGY [1–4]

Cancer of the large bowel is the second most important cancer in most of the developed countries in terms of both incidence and mortality. It affects with almost equal frequency the two genders. In developed countries there is neither clear secular trend nor marked socio–economic gradient, but in the developing countries the incidence is increasing and it is generally higher in the higher socio-economic groups and among urban residents. The international variation is large, with high values in western Europe and north America and low values in southeast Asia and Africa; migrant studies indicate that most of this variation is accounted for by environmental factors which appear to operate at relatively late stages of the natural history of the disease. Colorectal cancer is generally not viewed as an occupational disease, although increased rates have been reported among asbestos and textile workers and in sedentary occupations. A negative association with parity has been found in some but not all studies.

UNCOMMON CAUSAL FACTORS [1, 5–12]

Extensive ulcerative colitis of long duration and perhaps Crohn's disease are risk factors for colorectal cancer. Inherited adenomatosis is also an established nosological risk factor, as are several other less common genetic syndromes (mainly Gardner syndrome, Turcot syndrome and Peutz–Jeghers syndrome). Familial occurence may be noted even in 'sporadic' cases without identifiable premalignant pathology, whereas associations with several genetic markers have been reported but are not established. There is also evidence that colorectal cancer may be associated with *Schistosoma japonicum* infestation and with *Streptococcus bovis* bacteraemia, whereas venereally transmissible agents have been implicated in the etiology of squamous cell cancer of the rectoanal area. Several types of surgical operations have been reported to predispose to the development of colorectal cancer by affecting cell kinetics and modifying intestinal microflora; these include cholecystectomy and perhaps subtotal colectomy, jejuno–ileal bypass and ureterosigmoidostomy. Ionizing radiation has been shown to cause colorectal cancer in humans, whereas several chemicals including dimethylhydrazine, azoxymethane and methylazoxymethanol have been found to possess selective carcinogenic action in the intestinal mucosa of experimental animals. Finally there are theoretical reasons and limited empirical evidence that vitamin A, *b*-carotene, vitamin E, vitamin C, other anti-oxidants and selenium may have protective effects against several forms of cancer, including cancer of the large bowel.

EMPIRICAL EVIDENCE LINKING DIET TO COLORECTAL CANCER [11–15]

The results of most epidemiologic studies focusing on the association between diet and colorectal cancer appear to fall into one of two broad categories: those indicating that fat (mainly animal fat) and meat (particularly beef meat, which is an important source of fat in most developed countries) are conducive to the development of colorectal cancer, and those suggesting that vegetables or, more generally, fibre-containing food protect against the development of this cancer. Thus, among ecological studies four out of five have shown a positive correlation of colorectal cancer incidence with per capita meat consumption, three out of five a positive correlation with per capita consumption of total fat, and five out of seven a negative correlation with per capita consumption

of fibre. Among case-control studies six out of nine have shown a positive association of colorectal cancer with frequency of meat consumption, five out of seven a positive association with frequency of consumption of food high in (saturated) fats, and six out of eight a negative association with frequency of consumption of food high in fibre. The results of three cohort studies have not been generally supportive of either of these two hypotheses, although in Japan, high intake of rice and wheat (both of which are high in fibre) is associated with low incidence of colorectal cancer. In addition to dietary patterns, alcoholic beverages drinking habits have also been studied. A positive correlation between beer drinking and cancer of the rectum has emerged in several ecologic studies but the results of most analytic studies were not supportive of the existence of an association.

POSTULATED PATHOGENESIS OF DIET-RELATED COLORECTAL CANCER [11, 12, 16–21]

Carcinoma in the large bowel may develop through the stage of adenomatous polyp or it may develop through *de novo* occurrence of dysplastic changes in the colonic mucosa. Whichever the case, it is widely assumed that most dietary factors, including fat and fibre, operate as late promoters or progressors, rather than as initiators, in the long natural history of colorectal cancer. High-fat diet may act by increasing the biliary secretion of acid and neutral steroids and by modifying fecal bacterial flora and bacterial enzymatic activity (increasing the relative amounts of bacteroids, of anaerobes able to dehydroxylate bile acids, and particularly of nuclear dehydrogenating clostridia), thus leading to increased quantities and concentrations of secondary bile acids (e.g. dehydroxycholic acid) and degraded neutral steroids (e.g. coprostanol and coprostanone), and high ratios of cholesterol and its derivatives to plant sterols. Low-fibre diet may act by decreasing fecal bulk, by increasing transit time, and by modifying bacterial flora and enzymatic activity, thus increasing the quantity, the concentration and the mucosal contact of the various carcinogens (initiators and promoters) in the gut. There have been more than 12 ecologic studies exploring one or more aspects of the postulated pathogenic mechanisms; the collective evidence strongly suggests that secondary bile acids and nuclear dehydrogenating clostridia characterize populations at high risk for colorectal cancer, whereas the evidence concerning neutral steroids and other elements of the bacterial spectrum is inconclusive.

ACCOUNTING FOR INCONSISTENSIES

There are several reasons for the frequently 'negative' and occasionally conflicting results of epidemiologic studies focusing on the dietary etiology of colorectal cancer. They may be classified into 10 categories, as follows: (1) The 'instruments' for the ascertainment of diet (e.g. dietary questionnaires) are not sufficiently powerful; therefore, random misclassification of suspected dietary causal factors may be extensive leading to underestimation of true effects and, occasionally, to 'false negative' results. (2) Random misclassification of dietary factors may lead to inadequate control of their mutual confounding effects. Since confounding among food items and food groups is frequently negative, inadequate control may also generate 'false negative' results. (3) Small (undetectable with existing methods) variations in dietary intake (e.g. of fat) may be associated with large variations in the bacterial microflora and enzymatic activity, because of the dynamic nature of the latter two factors. (4) The dose–response curve describing colorectal cancer risk as a function of a particular dietary variable may be 'sigmoid', implying the existence of a lower and an upper 'threshold', below which and above which, respectively, there is no further association between the two variables. (5) If two factors are jointly necessary for the causation of colorectal cancer (e.g. an unknown initiator and a particular food item or dietary pattern as promoter) then the relative risk associated with one of the factors becomes a function of the population prevalence of the other [22]. Therefore, when the initiator in a certain population is very rare the relative risk associated with the particular diet (e.g. high-fat diet) becomes very close to 1, even if this diet is biologically critical for the development of the cancer [12]. (6) When many dietary factors are examined in a particular study then the 'multiple comparisons' can generate 'false negative' as well as 'false positive' results. (7) Many food items which are strongly intercorrelated may have independent but converging effects on colorectal cancer risk. In this situation adequate control of confounding becomes both critical and difficult requiring sophisticated statistical expertise which is not always available. Furthermore, negative confounding is frequently present and tends to obscure the full range of risk differentials associated with diet. The construction of a composite dietary risk score and the study of its frequency distribution can perhaps resolve this particular problem but the procedure is neither simple nor faultless [13, 23]. (8) In case-control studies the assumed latency of the diet-related carcinogenic effects may be incorrect, introducing substantial misclassification and biased estimations. (9) In cohort studies the dietary variability 'between individuals' may be too small in comparison to the variability 'between time-units' (e.g.

days or weeks) which form the temporal frame of reference for the ascertainment of the dietary habits. (10) Perhaps more important than anything else, in many developed countries the nutrition is too uniform and etiologically important food items are too common or too uncommon to permit identification and substantiation of risk differentials with analytic epidemiologic studies (case-control or cohort). Indeed, since nutritional variability is frequently greater between than within populations, ecologic studies may occasionally be more useful than analytic epidemiologic studies in identifying particular associations between diet and disease [24].

REFERENCES

1. Schottenfeld D, Winawer SJ. Large intestine. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention.* Philadelphia, WB Saunders, 1982, pp. 703–727.
2. Papadimitriou C, Day N, Tzonou A, Gerovassilis F, Manousos O, Trichopoulos D. Biosocial correlates of colorectal Cancer in Greece. *Int J Epidemiol* 1984, **13**, 155–159.
3. Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. *Am J Epidemiol* 1984, **119**, 1005–1014.
4. Vobecky J, Devroede G, Caro J. Risk of large-bowel cancer in synthetic fiber manufacture. *Cancer* 1984, **54**, 2537–2542.
5. Sales DJ, Kirsner JB. The prognosis of inflammatory bowel disease. *Arch Intern Med* 1983, **143**, 294–299.
6. Xu Z, Su DL. *Schistosoma japonicum* and colorectal cancer: an epidemiological study in the People's Republic of China. *Int J Cancer* 1984, **34**, 315–318.
7. Friedrich IA, Wormser GP, Gottfried EB. The association of remote *Streptococcus bovis* bacteremia with colonic neoplasia. *Am J Gastroenterol* 1982, **77**, 82–84.
8. Austin DF. Etiological clues from descriptive epidemiology: squamous carcinoma of the rectum or anus. *Natl Cancer Inst* Monogr 1982, **62**, 89–90.
9. Sandler RS, Sandler DP. Radiation-induced cancers of the colon and rectum: assessing the risk. *Gastroenterology* 1983, **84**, 51–57.
10. Weiss NS, Dalin JR, Chow WH. Cholecystectomy and the incidence of cancer of the large bowel. *Cancer* 1982, **49**, 1713–1715.
11. Willet WC, MacMahon B. Diet and cancer—an overview. *N Engl J Med* 1984, **310**, 633–638 and 697–701.
12. Zaridze DG. Environmental etiology of large-bowel cancer. *JNCI* 1983, **70**, 389–400.
13. Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A. Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer* 1983, **32**, 1–5.
14. Miller AB, Howe GR, Jain M, Craib KJ, Harrison L. Food items and food groups as risk factors in a case-control study of diet and colo-rectal cancer. *Int J Cancer* 1983, **32**, 155–161.
15. Stemmermann GN, Nomura AM, Heilbrun LK. Dietary fat and the risk of colorectal cancer. *Cancer Res* 1984, **44**, 4633–4637.
16. Hill MJ. Bacteria and the etiology of colonic cancer. *Cancer* 1974, **34**, 815–818.
17. Aries V, Growther JS, Drasar BS, Hill MJ, Williams RE. Bacteria and the actiology of cancer of the large bowel. *Gut* 1969, **10**, 334–335.
18. Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer* 1971, **28**, 3–13.
19. Turzman N, Goodman GT, Jaeger B, Nair PP. Diet, nutrition intake, and metabolism in populations at high and low risk for colon cancer. Metabolism of bile acids. *Am J Clin Nutr* 1984, **40**, 937–941.
20. Nomura AM, Wilkins TD, Kamiyama S *et al.* Fecal neutral steroids in two Japanese populations with different colon cancer risks. *Cancer Res* 1983, **43**, 1910–1913.
21. Reddy BS, Ekelund G, Bohe M, Engle A, Domellof L. Metabolic epidemiology of colon cancer: dietary pattern and fecal sterol concentrations of three populations. *Nutr Cancer* 1983, **5**, 34–40.
22. Rothman KJ. Causes. *Am J Epidemiol* 1976, **104**, 587–592.
23. Breslow NE, Day NE. *Statistical Methods in Cancer Research*, Vol. 1. *The Analysis of Case-Control Studies.* IARC Scientific Publications No 32, International Agency for Research on Cancer, Lyon, 1980.
24. Doll R, Peto R. The causes of cancer. JNCI 1981, **66**, 1191–1308.