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Large Bowel Adenomas: Markers of Risk and Endpoints

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Abstract In many large bowel chemoprevention trials adenomas have a double duty: they are used to identify subjects at risk for large bowel neoplasia, and also serve as endpoints. Many features of adenomas make them suitable for these tasks. Patients with adenomas are fairly numerous and easy to identify; further, the 'adenoma-carcinoma' sequence suggests that adenomas are logical endpoints. The high recurrence risk among adenoma patients means that a relatively modest number of subjects will suffice for adequate statistical power.

The are some limitations to the use of adenomas, however. There is clearly heterogeneity of risk for subsequent cancer. Patients with only small adenomas may have rates of colorectal cancer that are not much greater than those of the general population. Certainly subjects with larger adenomas, and those with villous or highly dysplastic adenomas have a higher risk. Often, one would chose the high-risk patients for preventive interventions. Such a strategy makes sense from a risk-benefit point of view. However, from a population perspective, such a strategy may well have only a minor impact on the overall colorectal cancer burden. For more complete population-based prevention, efforts will have to be directed to the numerous individuals who are each at small risk, but who collectively account for most colorectal cancer. For this preventive approach, patients with any adenoma would certainly be part of the target population, and so are sensible subjects in chemoprevention trials.

There are similar complexities in consideration of the use of adenomas as endpoints of chemoprevention trials. The adenomas that occur in prevention trials are generally small, and may not be associated with a greatly increased cancer risk. The issue for chemoprevention trials, however, is not whether the endpoints are truly intermediate in the causal chain—but whether the intervention under study alters the adenoma recurrence risk to the same extent as it does for colorectal cancer risk. This is a difficult matter to verify, but the limited data available are encouraging. The epidemiology of colorectal adenomas (largely small adenomas) is similar in many regards to that for colorectal cancer itself. Thus to the extent that data are available, one can tentatively conclude that external influences affect adenomas and colorectal cancer similarly.

To date, more than ten adenoma prevention trials have reported results. The data have been fairly consistent. Vitamin C (with or without vitamin E) has provided at most a modest protective benefit, except in one small trial in which it was combined with vitamin E and preformed vitamin A. β-Carotene seems to be without any effect, and interventions to increase fiber and decrease fat intake have not indicated substantial effects. On the other hand, trials among familial polyposis patients have provided evidence for an impact of nonsteroidal anti-inflammatory drugs. Studies in progress have the potential to clarify greatly the preventive potential of the currently promising—but yet unproven—chemopreventive regimens. J. Cell. Biochem. 25S: 142–148. © 1997 Wiley-Liss, Inc.

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For the investigation of possible preventive agents for large bowel cancer, the ideal study would be a large trial using cancer itself as the endpoint. Unfortunately, such trials can rarely be done. It is likely that large numbers of subjects would need to be observed for long periods of time, requirements which imply considerable expense and difficulty. The prolonged observation introduces difficulties of competing risks and drop-outs, and there may be pressure to terminate the study early if the agent under study has beneficial effects other than a protective effect on large bowel cancer.

For the large bowel, adenomas are convenient intermediate endpoints that offer the potential for studies which avoid these difficulties. A substantial number of chemoprevention trials using adenomas as endpoints have been, or are currently being, conducted. A unique feature of many of these trials is that the princi-

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pal entry criteria (adenomas) is also the principal endpoint. This dual role raises several interesting issues for the conduct and interpretation of this research.

ADENOMAS AS AN ENTRY REQUIREMENT

Patients with sporadic adenomas are attractive subjects for large bowel chemoprevention trials. They have all successfully experienced endoscopy, and in general accept the procedures used for adenoma surveillance. Typically, these patients have already been educated about adenomas and colorectal cancer by their physicians. Because of the increased risk of neoplasia associated with a history of adenomas, follow-up surveillance is usually arranged as part of routine clinical care.

The risk of further adenomas in patients who have had at least one is relatively high. In the National Polyp Study approximately 32% of adenoma patients had at least one adenoma when examined 3 years later [1], and in the Antioxidant Polyp Prevention Study, 37% of subjects had an adenoma during the 3-year risk period [2]. This high event rate permits informative adenoma trials to be conducted with a relatively small number of subjects, often less than 1,000. Among patients with familial adenomatous polyposis (FAP), the very high adenoma burden implies that even smaller numbers will suffice.

The convenience of adenoma patients as subjects is clear. However, recruitment is far from automatic; even among these patients, considerable effort is required. Identification of the patients with adenomas is not a problem: this is typically quite easy in most medical centers. The difficulty is that only a minority of these patients may be eligible and willing to participate. In the Antioxidant Polyp Prevention Study [2], for example, less than 50% of patients identified as apparently eligible, actually met the entry criteria and were willing to be randomized.

Selection pressures such as these can have undesirable effects in clinical trials: healthy patients tend to be recruited, and they may have a low event rate. An example is the Physicians' Health Study, a large clinical trial among male doctors, testing aspirin and β-carotene as preventive agents against cardiovascular disease and cancer. Participants had such a low cardiovascular mortality (one eighth that of the general U.S. male population) that the trial had difficulty attaining its original aims [3]. The Colon Cancer Control Study was similarly affected. Participants in this trial of hemoccult screening for colorectal cancer had a standardized mortality ratio (SMR) from colorectal cancer of 0.55 in the first few years of the study, and an SMR of 0.72 in the later years. This lower-than-expected event rate forced an extension of the study [3].

For adenoma trials, however, the effects of the recruitment selection appear to be minimal. Before the Antioxidant Polyp Prevention Study began, a 30% 3-year recurrence risk was predicted, based on the then-available clinically generated recurrence data. The observed risk was actually slightly higher, 37% [2]. Fortunately, the selection factors associated with participation in the study were not associated with a lower adenoma recurrence risk.

The extra risk of cancer that adenoma patients face is not as straightforward as it first appears from consideration of the well-known adenoma-carcinoma sequence [4]. There are only limited clinical or epidemiological data documenting the relationship between a history of adenomas and the risk of subsequent colorectal cancer. In a study from England, patients with bowel symptoms (largely bleeding) who were discovered to have rectal adenomas (generally subsequently removed) had a relative risk of 1.2 (95% CI, 0.7–2.1) for rectal cancer and 2.1 (95% CI, 1.5–3.0) for colon cancer in comparison to population rates [5]. In Rochester, Minnesota, patients with polyps (largely adenomas) of the left colorectum had a relative risk of 1.7 for colorectal cancer in comparison to the general population [6–8]. These relative risks imply an increased risk of large bowel cancer, but clearly not a very greatly increased risk.

There is evidence, moreover, of heterogeneity of this risk. In the English study, patients that had only tubular adenomas less than 1 cm in diameter had a relative risk of 0.4 (95% CI, 0.0–1.3) for rectal cancer, and 0.5 (95% CI, 0.1–1.3) for colon cancer. The relative risks for those with larger or more dysplastic adenomas were 2.0 (95% CI, 1.0–3.6) and 3.6 (95% CI, 2.4–5.0), respectively [5]. In Rochester, patients with polyps less then 1 cm that were fulgurated or left in place had a relative risk of colorectal cancer of 1.2 (95% CI, 0.7–1.9), in contrast to 3.2 (95% CI, 1.5–6.1) for those at least one polyp greater than a 1 cm in diameter [6–8]. Villous appearance, and high grades of dysplasia also

are associated with increased risk. Adenomas are a general marker of risk even apart from the adenoma-carcinoma sequence: in both studies, the risk of cancer was increased in the proximal bowel—in areas remote from the original polyps [5–8].

These data are difficult to interpret. It is not clear what selection factors led to the discovery of the adenomas. For the English study particularly, the use of population rates for reference may not be appropriate. Consequently, the magnitude of the cancer risk associated with a history of adenomas cannot easily be estimated from the data. These uncertainties do not provide evidence against the heterogeneity of risk, however, and the data are rightfully taken to mean that small and large adenomas imply different degrees of risk of large bowel cancer.

Many patients in adenoma chemoprevention trials have relatively small adenomas. In the Antioxidant Polyp Prevention Study, approximately three-fourths of subjects qualified with adenomas 1 cm or less in diameter; in over half of the subjects the largest adenoma was less than 0.7 cm. Since these subjects do not have as high a cancer risk as patients with adenomas over 1 cm in diameter, are these inappropriate trial subjects?

Consideration of investigator convenience aside, the best patients for a prevention trial are probably individuals who resemble the patients who would use the interventions that are found to be effective. Unfortunately, there has been relatively little discussion of who the target groups should be for the proven agents. A general discussion has clear limitations; clarification of the appropriate target group will inevitably require consideration of the magnitude of the benefits and risks carried by the particular intervention in the specific context of the baseline risk of the group receiving the agent. However, some general considerations are relevant. For cancer of the large bowel, a broad population intervention is conceivable, but a focussed intervention toward a high-risk group is also likely to be recommended because of the favorable risk-benefit ratio among them.

In practical terms, how might such a high-risk group be constructed? Certainly risk factors for colorectal cancer could help: individuals with a family history of colorectal cancer, and those who have large or dysplastic adenomas are likely to be considered for preventive efforts. These individuals would clearly be appropriate subjects for large bowel chemoprevention trials.

However, most cases of colorectal cancer that might occur in the general population would probably be missed by this approach, since most cases occur among the very large segment of the population who individually have only a modest increase in risk [9]. Thus in order to reduce the population burden of colorectal cancer, it is likely that the large group of individuals with small adenomas would be included in the preventive effort. If so, these patients are clearly also appropriate subjects for the chemoprevention trials.

ADENOMAS AS ENDPOINTS

The studies evaluating adenomas as risk factors for frank cancer suggest that it is large sporadic adenomas that carry the risk—and therefore would be the best outcomes of large bowel chemoprevention trials. Unfortunately, in the trials conducted to date, the adenomas observed have been small—considerably less than the 1.0 cm. In the National Polyp Study less than 3% of the adenomas found on follow-up were greater than 1 cm in estimated diameter [1]. In The Antioxidant Polyp Prevention Study [2], about 90% of the adenomas observed after randomization were less than 1 cm, and more than 75% were 0.5 cm or less.

This predominance of small adenomas has generated some concern. However, for large bowel prevention trials, the issue is not whether subjects with small adenomas are at risk for cancer, but whether the small adenoma endpoints lead to the same conclusions that would be obtained using large adenomas (or better, frank invasive cancer) as the endpoint. What is required is for the intervention to affect the small adenomas in the same way it affects the risk of cancer.

The evidence regarding the effect of environmental factors on small adenomas is incomplete, but fairly encouraging. The epidemiology of adenomas has many similarities to that of colorectal cancer. Epidemiological studies of sporadic adenomas—generally small adenomas—have largely found the same dietary risk factors as investigations of colorectal cancer itself: high dietary fat intake, and low consumption of fruits and vegetables [10]. Folate has a similar relationship to adenoma occurrence as to colorectal cancer itself [11,12]. Use of aspirin seems similarly protective for both [13].

One interesting issue is cigarette smoking—which has been associated with the risk of adenomas in many—but not all—cross-sectional studies of adenoma prevalence, but has only inconsistently been related to colorectal cancer [14–16]. It has been hypothesized that smoking affects the very early stages of large bowel carcinogenesis: essentially the formation of small adenomas—and that only after a long latent period is this exposure related to cancer itself. Under this hypothesis, smoking actually affects adenomas and cancer similarly, with different latent periods. Thus, to the extent data is available, it appears that small adenomas are reasonable endpoints for large bowel chemoprevention trials.

There is some measurement error associated with the adenoma endpoint. Only a few percent of adenomas over 1 cm in diameter will be overlooked during a colonoscopy [17,18], but 15% or more of adenomas smaller than that might be missed. It is reasonable to assume, however, that there will be essentially no false positive adenomas—that is, that the pathologist will not label as an adenoma other lesions. This combination of very high specificity, and excellent, but not perfect, sensitivity has predictable implications for the relative risk estimates. Risk ratios are essentially unaffected by this sort of measurement error [19]. Because of the high event rate, odds ratios will not approximate risk ratios, and (assuming a non-differential error) a modest conservative bias may be introduced by the measurement error [20]. Studies conducted among FAP patients present more severe measurement difficulties. Counting the large numbers of adenomas in these patients may be prone to error; polyp area or volume scores cannot easily overcome that.

There remain uncertainties regarding the appropriate duration of treatment required for the trials. Some have argued that it may be necessary to begin treatment early in life, or that prolonged interventions may be required [21]. This appears not to be the case for aspirin—where use in the few years before diagnosis seems to be the relevant exposure [13]. It is admittedly not clear that the same can be said of other interventions (e.g., folate or calcium supplementation, or dietary change). The large bowel mucosa is a rapidly renewing tissue [22]; 3 or 4 years of treatment may be long enough for a clinically significant suppression of early neoplasia, but a longer duration may also be necessary.

FINDINGS OF ADENOMA PREVENTION TRIALS

There are more than ten adenoma prevention trials that have reported results, at least in abstract form. Some have followed adenoma mass among patients with familial polyposis; others have focussed on sporadic adenoma occurrence. The data have been fairly consistent.

In five trials, vitamin C (with or without vitamin E) has provided at most a modest protective benefit (Table I). One of these was a 4-study among subjects with sporadic adenomas; vitamin C (1 gm daily) and vitamin E (400 mg daily) were used in combination. There was no beneficial effect on adenoma occurrence [2]. Another 4-trial of vitamins C and E in combination (4 gms and 400 mg respectively), was conducted among subjects with familial polyposis [23]; there were no benefits from the vitamin administration. A 2-year trial among subjects with sporadic adenomas also found no substantial effect for vitamin C (400 mg) and vitamin E (400 mg) together: the relative risk for the vitamin group was 0.97 (95% CI, 0.51–1.84) [24]. A 2-year trial among patients with familial polyposis found hints of a modest benefit [25]. In contrast, a smaller trial focusing on sporadic adenomas found a substantial effect for vitamins C and E combined with retinol (preformed vitamin A). The study lasted a shorter time than the negative trials, and had a relatively high drop-out rate. Epidemiological studies do not suggest that retinol is protective against large bowel neoplasia [27], and so it is difficult to accommodate this result into the human epidemiology of colorectal neoplasia and the other findings.

β-Carotene was without effect in three trials among patients with sporadic adenomas: the 18-month interim analysis of a 3-year study [28], and two other 4-year investigations [2,29] (Table I). Two trials of interventions to increase dietary fiber and decrease fat intake have also been reported (Table II) [29,30]. Both were modestly sized trials conducted among patients with sporadic adenomas. Neither study reported an overall benefit, although the Australian trial reported suggestions of a beneficial effect of a low-fat diet on the occurrence of adenomas at least one cm in diameter [29]. A trial of cereal supplementation in patients with familial pol-

TABLE I. Chemoprevention Trials of Micronutrients and Large Bowel Neoplasia

	Number of subjects entered (completed); duration of treatment	Intervention	Relative risk for intervention (95% confidence interval)
Patients with Sporadic Adenomas			
McKeown-Eyssen et al., 1988 [24]	185 (137) subjects; 2 years	Vitamin C, 400 mg & Vitamin E, 400 mg	0.93 (0.48, 1.83)
Kikendall et al., 1990 [28]	262 subjects; 1.5 years (interim analysis)	β-Carotene, 15 mg	No significant effect
Roncucci et al., 1993 [27]	255 (209) subjects; 1.5 years (average)	Vitamin C, 1 gm, Vitamin E, 70 mg, Retinol, 30,000 IU	0.13 (ratio of numbers of adenomas)
Greenberg et al., 1994 [2]	864 (751) subjects; 4 years	Vitamin C, 1 gm & Vitamin E, 400 mg	1.01 (0.85–1.20)
		β-Carotene, 25 mg	1.08 (0.91–1.29)
Macrae et al., 1995 [29]	424 subjects; 4 years	β-Carotene, 20 mg	1.3 (0.8–2.2)
Paspatis et al., 1994 [31]	60 subjects; 2 years	Folate 1 mg	0.46
Patients with Familial Polyposis			
Bussey et al., 1982 [25]	49 (36) subjects; 2 years	Vitamin C, 3 gm	0.7 (Ratio of area scores)
DeCosse et al., 1989 [23]	72 (58) subjects; 4 years	Vitamin C, 4 gm Vitamin E, 400 mg	inconsistent, non-significant benefit

TABLE II. Trials of High Fiber/Low Fat Diet and Large Bowel Neoplasia

	Number of subjects entered (completed); duration of treatment	Intervention	Relative risk for intervention (95% confidence interval)
Patients with Sporadic Adenomas			
Macrae et al., 1995 [29]	424 subjects; 4 years	<25% fat calories	0.9 (0.5–1.5)
		25 gm wheat bran-supplement	1.5 (0.9, 2.5)
McKeown-Eyssen et al., 1994 [30]	201 (165) subjects; 2 years (average)	<50 gm fat or 20% fat calorie, and 50 gm fiber	1.2 (0.6, 2.2)
Patients with Familial Polyposis			
DeCosse et al., 1989 [23]	72 (58) subjects; 4 years	22.5 gm cereal fiber Vitamin C, 4 gm Vitamin E, 400 mg	Consistent, but non-significant benefit versus placebo and vitamins alone

TABLE III. Chemoprevention Trials of Non-Steroidal Anti-Inflammatory Drugs and Large Bowel Neoplasia

	Number of subjects entered (completed); duration of treatment	Intervention	Effect
Patients with Familial Polyposis			
Labayle et al., 1991 [32]	10 (9) patients-cross-over; 4 months	Sulindac, 300 mg	Dramatic decrease in number and size of polyps on treatment
Giardiello et al., 1993 [33]	22 (20) patients; 9 months	Sulindac, 300 mg	66% Reduction in number of polyps on treatment

yposis found a reduction in adenoma mass in association with the fiber intervention [23]. A very small trial of folate supplementation yielded findings supportive of a protective effect, but the limited power of the study precludes strong conclusions [31].

In contrast to this mixed picture, non-steroidal anti-inflammatory drugs have been very promising (Table III). Two randomized trials of sulindac have been published, using patients with FAP [32,33]. Both found evidence for a marked reduction of adenomas on treatment. In patients with sporadic adenomas, sulindac may not be dramatically effective in causing existing adenomas to regress [34]; the effect on the occurrence of the adenomas is currently under investigation in trials.

Unfortunately, the interpretation of these trials is not completely straight-forward. Some of the problems are biological. Findings for familial polyposis patients may not apply to the mass of individuals at risk for sporadic colorectal cancer. There are also epidemiological problems. In many of these trials, subjects can obtain the study agents freely in grocery stores, complicating the maintenance of trial discipline, and raising the issue of false-negative results. Drop-out rates were relatively high in some of the studies, possibly because of the burden of endoscopy and other efforts needed among subjects who are not very ill. Small sample size affects most of the negative studies, and some of the data reported pertain only to very short duration of treatment and follow-up. Substantial measurement difficulties remain from the counting of adenomas in familial polyposis patients, and the problem of overlooked adenomas in other patients. For trials involving major dietary change, assessment of compliance introduces analytical problems. These consideration generally imply conservative biases, however, so it is reasonable to be encouraged by the clear indications of benefit from non-steroidal antiinflammatory drugs, and the suggestions of benefit from fiber. Several chemoprevention trials are currently underway, and the scientific and clinical community can look forward to further clarification of the effect of several potential chemopreventive interventions.

REFERENCES

1. Winawer SJ, Zauber AG, O'Brien MJ, Ho MN, Gottlieb L, Sternberg SS, Waye JD, Bond J, Schapiro M, Stewart ET, Panish J, Ackroyd F, Kurtz RC, Shike M, and the National Polyp Study Workgroup (1993): Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. N Engl J Med 328:901–906.
2. Greenberg ER, Baron JA, Tosteson TD, Freeman Jr DH, Beck GJ, Bond JH, Colacchio TA, Coller JA, Frankl HD, Haile RW, Mandel JS, Nierenberg DW, Rothstein R, Snover DC, Stevens MM, Summers RW, van Stolk RU (1994): A clinical trial of antioxidant vitamins to prevent colorectal adenoma. N Engl J Med 331:141–147.
3. Ederer F, Church TR, Mandel JS (1993): Sample sizes for prevention trials have been too small. Am J Epidemiol 137:787–796.
4. Muto T, Bussey HJR, Morson BC (1975): The evolution of cancer of the colon and rectum. Cancer 36:2251–2270.
5. Atkin WS, Morson BC, Cuzick J (1992): Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 326:658–662.
6. Spencer RJ, Melton LJ, Ready RL, Ilstrup DM (1984): Treatment of small colorectal polyps: A population-based study of the risk of subsequent carcinoma. Mayo Clin Proc 59:305–310.
7. Lofti AM, Spencer RJ, Ilstrup DM, Melton LJ (1986): Colorectal polyps and the risk of subsequent carcinoma. Mayo Clin Proc 61:337–343.
8. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL (1987): Natural history of untreated colonic polyps. Gastroenterology 93:1009–1013.
9. Rose G (1981): Strategy of prevention: Lessons from cardiovascular disease. Brit Med J 282:1847–1851.
10. Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC (1992): Relationship of diet to risk of colorectal adenoma in men. J Natl Cancer Inst 84:91–98.
11. Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, Speizer FE, Willett WC (1993): Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 85:875–884.
12. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC (1995): Alcohol, low-methionine—low- folate diets, and risk of colon cancer in men. J Natl Cancer Inst 87:265–273.
13. Baron JA (1995): Aspirin and cancer. Prev Med 24:121–124.
14. Neugut AI, Jacobson JS, DeVivo I (1993): Epidemiology of colorectal adenomatous polyps. Cancer Epidemiol Biomarkers Prev 2:15–17.
15. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Kearney J, Willett WC (1994): A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst 86:183–191.
16. Giovannucci E, Colditz GA, Stampfer MJ, Hunter D, Rosner BA, Willett WC, Speizer FE (1994): A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. J Natl Cancer Inst 86:192–199.
17. Hoff G, Vatn M (1985): Epidemiology of polyps in the rectum and sigmoid colon. Scand J Gastroenterol 20: 356–360.
18. Hixson LJ, Fennerty MB, Sampliner RE, McGee D, Garewal H (1990): Prospective study of the frequency and size distribution of polyps missed by colonoscopy. J Natl Cancer Inst 82:1769–1772.

19. White E (1986): Effect of misclassification of disease status in follow-up studies: Implications for selecting disease classification criteria. Am J Epidemiol 124:816–825.
20. Goldberg JD (1975): The effects of misclassification on the bias in the difference between two proportions and the relative odds in the fourfold table. J Am Stat Assoc 70:561–567.
21. Lipkin M, Newmark H (1995): Development of clinical chemoprevention trials. J Natl Cancer Inst 87:1275–1277.
22. Simanowski UA, Wright NA, Seitz HK (1989): Mucosal cellular regeneration and colorectal carcinogenesis. In Seitz HK, Simanowski UA, Wright NA (eds): "Colorectal Cancer: From Pathogenesis to Prevention?" London: Springer-Verlag, pp 225–236.
23. DeCosse JJ, Miller HH, Lesser ML (1989): Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. J Natl Cancer Inst 81:1290–1297.
24. McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P, Bruce WR (1988): A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. Cancer Res 48:4701–4705.
25. Bussey HJR, DeCosse JJ, Deschner EE, Eyers AA, Lesser ML, Morson BC, Ritchie SM, Thomson JPS, Wadsworth J (1982): A randomized trial of ascorbic acid in polyposis coli. Cancer 50:1434–1439.
26. Roncucci L, Di Donato P, Carati L, Ferrari A, Perini M, Bertoni G, Bedogni G, Paris B, Svanoni F, Girola M, Ponz de Leon M (1993): Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. Dis Colon Rectum 36:227–234.
27. Boutron MC, Wilpart M, Jaivre J (1991): Diet and colorectal cancer. Eur J Cancer Prev 1 (Suppl):13–20.
28. Kikendall JW, Burgess M, Bowen PE (1990): Effect of oral beta carotene on recurrence of colonic adenomas. Gastroenterology 98:A289.
29. MacLennan R, Macrae F, Bain C, Battistutta D, Chapuis P, Gratten H, Lambert J, Newland RC, Ngu M, Russell A, Ward M, Wahlqvist ML, and the Autralian Polyp Prevention Project (1995): Randomized trial of fat, fiber and beta carotene to prevent colorectal adenomas. J Natl Cancer Inst 87:1760–1766.
30. McKeown-Eyssen GE, Bright-See E, Bruce WR, Jazmaji V, and the Toronto Polyp Prevention Group (1994): A randomized trial of a low fat high fibre diet in the recurrence of colorectal polyps. J Clin Epidemiol 47: 525–536.
31. Paspatis G, Xourgias B, Mylonakou E, Aisis D, Barbagianis G, Karamanolis D (1994): A prospective clinical trial to determine the influence of folate supplementation on the formation of recurrent colonic adenomas. Gastroenterology 106:A425.
32. Labayle D, Fischer D, Vielh P, Drouhin F, Patiente A, Bories C, Duhamel O, Trousset M, Attali P (1991): Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 101:635–639.
33. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, Booker SV, Robinson CR, Offerhaus GJA (1993): Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 328:1313–1316.
34. Hixson LJ, Earnest DI, Fennerty MB, Sampliner RE (1993): NSAID effect on sporadic colon polyps. Am J Gastroenterol 88:1652–1656.