

COMMENTARY

Interpreting Precursor Studies: What Polyp Trials Tell Us About Large-Bowel Cancer

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Research scientists and clinicians who study and treat large-bowel cancer have initiated several clinical trials to examine the effects of pharmacologic and nutritional interventions on adenomatous polyp recurrence. Typically, in these trials, persons with recently resected adenomatous polyps are randomly allocated to receive either an experimental intervention or standard surveillance, and the subsequent rates of adenoma recurrence in the two groups are measured and compared. A so-called polyp trial is substantially smaller and shorter (and therefore less expensive) than an analogous intervention study in which large-bowel cancer is the end point. The implicit assumption driving the conduct of polyp trials is that inferences about the effects of an intervention on the prevention of large-bowel cancer can be made by examining the effects of this intervention on adenoma recurrence.

In this commentary, we examine this assumption by analyzing the possible inferences that can be drawn from polyp trial findings.

Recurrent Adenomas as End Points: Rationale

There are several strong arguments for undertaking polyp trials.

1) High prevalence. The prevalence of adenomatous polyps in the populations of industrialized countries, though difficult to determine precisely, is undoubtedly high. Autopsy studies suggest a prevalence of over 50% in some older age groups (1). The relatively high prevalence of large-bowel adenomas ensures a reasonably large pool of potential participants for prevention trials.

2) High recurrence rate. The recurrence rate of large-bowel adenomas is high—in the range of 10% or more annually (1). ("Recurrence" is defined here as the development of a new adenomatous polyp anywhere in the large bowel subsequent to identification and removal of one or more "index" [base-line] adenomas.) Because the adenoma recurrence rate is about 1-2 orders of magnitude greater than the incidence rate of large-bowel cancer, an intervention study with recurrent adenomas as end points requires a sample size much smaller than that needed in a trial with incident large-bowel cancer as the end point.

3) The adenoma-carcinoma sequence. Although only a small proportion of adenomatous polyps become malignant, adenomas are generally considered obligate precursors of most large-bowel cancers (2). In other words, adenomas are a necessary intermediate end point (3) in large-bowel carcinogenesis. Abundant clinical, pathologic, and epidemiologic data support the concept of an adenoma-carcinoma sequence (4); cell biologic (5) and molecular genetic findings (6) have extended this evidence. Hill (7) has argued that it may be more accurate to speak of a "dysplasia-carcinoma sequence" because malignant transformation of dysplastic foci may occur before much polypoid "heaping" takes place. All adenomas contain dysplastic epithelial tissue, however, and it seems reasonable to retain the clinically useful, if less pathologically precise, notion of the adenoma-carcinoma sequence.

4) Integration of standard clinical practice into study designs. Standard postpolypectomy surveillance has involved one or more repeat colonoscopies. This surveillance approach affords investigators the opportunity to examine the study participants for recurrent adenomas as part of standard clinical practice and thereby ascertain the study end points. We note, however, that the required number of participants in a polyp trial depends, in part, on the number and frequency of follow-up colonoscopic procedures. Shifts in clinical practice with regard to the frequency of follow-up colonoscopy (8) will therefore mandate alterations in polyp trial design.

Making Inferences From Adenoma Recurrence Trials to Large-Bowel Cancer

The goal of the interventions used in polyp trials is not only to lower adenoma recurrence but also to inhibit the development of adenomas with malignant potential. The motivating assumption

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See "Note" section following "References."

tion of research efforts in polyp trials is that a decrease in observed adenoma recurrence truly reflects a consequent reduction in those polyps with malignant potential, which in turn implies a lowered incidence of large-bowel cancer.

It is clear that some adenomas are more likely to develop into malignant lesions than others. For example, the risk of malignancy increases with the size of the adenomatous polyp and villous adenomas are more likely than their tubular counterparts to become malignant (8). With present knowledge, we can do no more than crudely assign a gradation of malignant potential to each adenoma. For the purposes of discussion, however, we assume that certain ("innocent") adenomatous polyps have no potential to develop malignancy whereas other ("bad") adenomas do. We do not know for sure that this is the case. If it is not, then reducing the number of polyp recurrences must reduce the number of cancers. Only if we assume correctly that there is a pool of innocent adenomas with no malignant potential is there a possible problem with interpretation, as discussed below.

As we consider the appropriate inferences to be drawn from the (observed) adenoma findings in a polyp trial, we will refer, for illustrative purposes, to the ongoing Polyp Prevention Trial (9). This trial is a multicenter nutritional intervention study of adenoma recurrence. Participants, all of whom must have had one or more adenomas recently removed, undergo repeat colonoscopy at 1 (T1) and 4 (T4) years after the index polypectomy. To achieve the dietary targets of consuming 20% of calories from fat, 18 g of dietary fiber per 1000 kcal, and five to eight servings of vegetables and fruit daily, the intervention group (n = 1000) receives intensive nutritional and behavioral counseling to facilitate the adoption of an eating plan that is low in fat and high in fiber, fruits, and vegetables. The control group (n = 1000) receives no special nutritional or behavioral instruction. The trial has 90% power to detect a 24% reduction in polyp recurrence over a 3-year period (from T1 to T4). Because some polyps may be missed at base line, the T1 colonoscopy is considered the definitive clearing procedure and the primary analytic interval is T1 through T4. This analytic interval also allows for a lag time of 1 year for the dietary modification to achieve a substantial preventive effect.

Inferential Implications of a Positive Finding

Let us now consider the possible inferences that can be drawn from a positive result (i.e., a statistically significant reduction in adenoma recurrence in the intervention group compared with the control group) in the Polyp Prevention Trial. Two inferences about large-bowel cancer can be drawn from this adenoma finding (Fig. 1).

1) Primary inference. The intervention reduces the incidence of large-bowel cancer incidence (by decreasing the development of adenomas with malignant potential).

2) Alternative inference. The intervention reduces the development of innocent adenomas without malignant potential but has no effect on the occurrence of bad adenomas with malignant potential. Therefore, the intervention does not reduce large-bowel cancer incidence.

To put it another way, the primary inference assumes that the intervention has a nondifferential effect on bad and innocent adenomas. The alternative inference posits a differential effect of the intervention on these two types of adenomas.

The alternative inference from a positive finding in a polyp trial may be speculative at best, but we cannot exclude it entirely. Although reductions in number, size, and degree of dysplasia of recurrent adenomas would suggest a diminution of bad polyps in the intervention group, one could still argue that the number of participants with adenomas that contain specific molecular genetic lesions necessary for malignant transformation might be as great in the intervention group as in the control group. Because specific and necessary adenoma-transforming molecular lesions have not been definitively identified, it is not possible at present to determine whether there really are innocent and bad adenomas, distinguish the bad polyps, or compare the recurrence of the bad polyps in the intervention and control groups.

Inferential Implications of a Null Finding

We now turn to the possible inferences drawn from a null finding—equal rates of polyp recurrence in intervention and control groups—in a polyp trial that is like the Polyp Prevention Trial. Several inferences can be drawn from such a null finding.

Primary inference. The intervention does not reduce large-bowel cancer incidence.

Alternative inference #1. The intervention reduces the development of bad adenomas but has no effect on the genesis of innocent adenomas (which might constitute the majority of polyps). The intervention therefore does lower the incidence of large-bowel cancer, even though a statistically significant reduction in total adenoma recurrence is not observed.

Alternative inference #2. The intervention does not affect the development of small adenomas but does affect the growth of small adenomas into large adenomas, which are more prone to develop into carcinomas. Therefore the intervention does decrease large-bowel malignancies.

Alternative inference #3. The intervention was administered for an insufficient length of time. A longer period of intervention would have revealed a positive trial result, that is, reduced adenoma recurrence.

Alternative inference #4. Follow-up time, which could include a period of postintervention observation, was inadequate. A positive trial finding would have emerged with longer follow-up.

Alternative inference #5. The intervention reduces bad polyps (and cancer incidence) only when it is administered in early life.

We now consider each of these inferences. The primary inference and alternative inference #1 for a null finding are depicted in Fig. 2. In alternative inference #1, the intervention does not affect the vast majority of adenomas, which are without malignant potential, but does reduce the recurrence of those bad adenomas that lead to cancer. Because the intervention affects the small minority of bad adenomas, one would observe some overall reduction in polyp recurrence, but it would be unlikely to achieve statistical significance if the proportion of bad

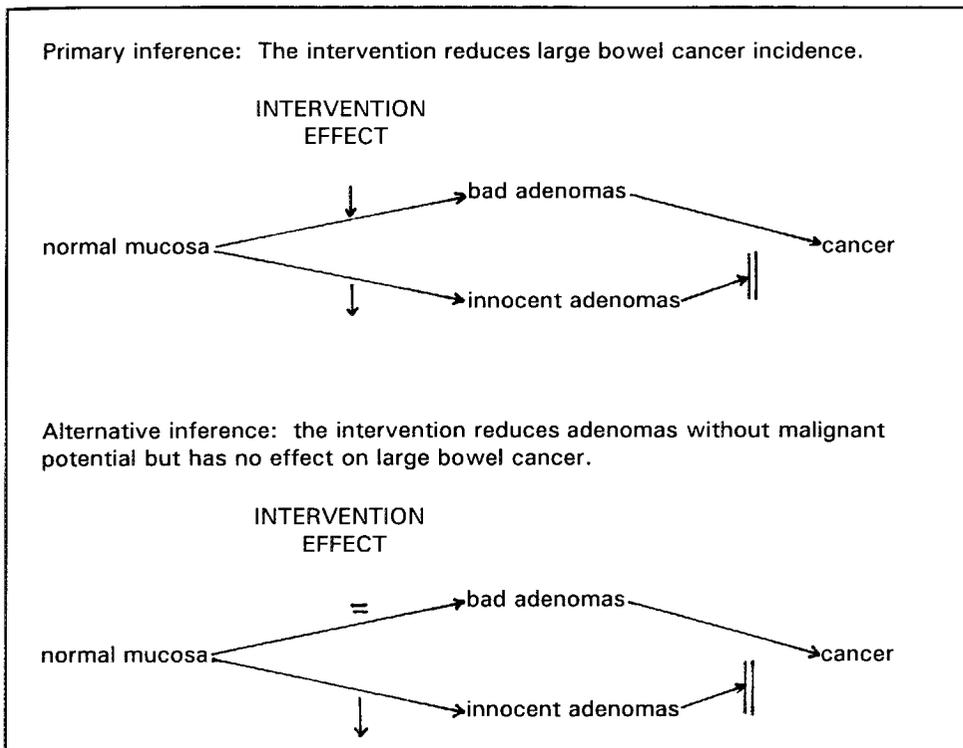


Fig. 1. Possible inferences from a positive polyp trial result. Innocent adenoma = without malignant potential; bad adenoma = with malignant potential. (=) = no effect; (↓) = inhibitory (preventive) effect.

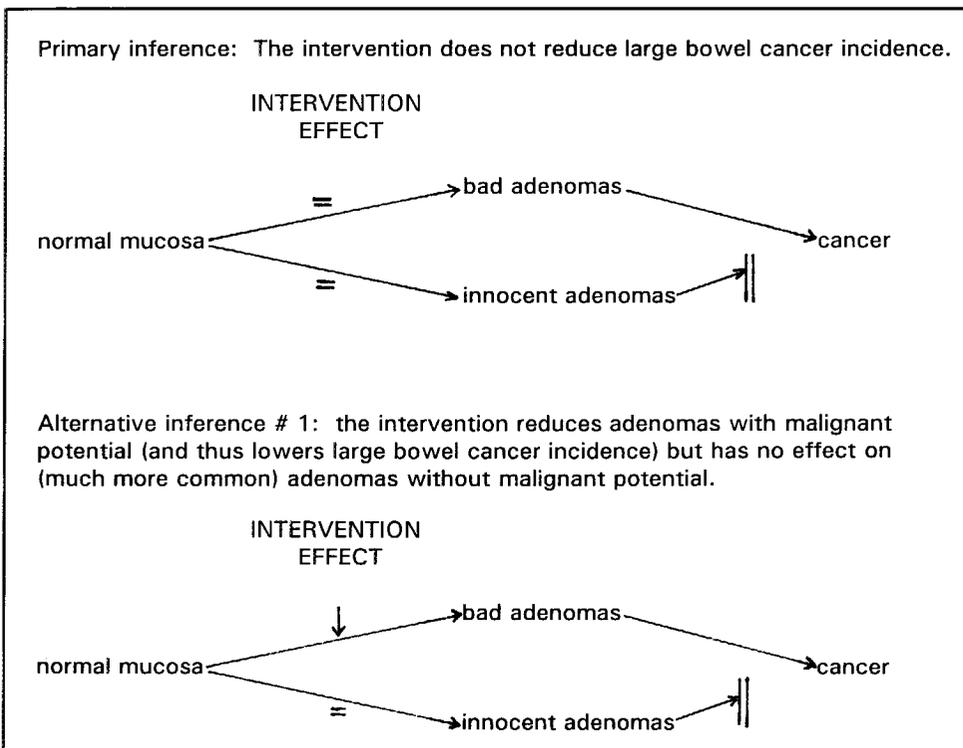


Fig. 2. Possible inferences from a null polyp trial result. Innocent adenoma = without malignant potential; bad adenoma = with malignant potential. (=) = no effect; (↓) = inhibitory (preventive) effect.

adenomas were small. This inference is clearly analogous to the alternative inference from a positive finding. It is also hypothetical.

Alternative inference #2 is predicated on a particular model of large-bowel carcinogenesis proposed by Hill et al. (10). This model presupposes distinct steps in the development of neoplasia in the large intestine (Fig. 3). The key issue is at

which step(s) the intervention operates. If step A (from normal mucosa to small adenoma) were influenced only by genetic or other factors that are not related to the intervention, whereas if step B (from small to large adenoma) were modulated by the intervention, then a clinical trial that examined the effect of an intervention on polyp recurrence—i.e., growth of small polyps from normal epithelium—would fail to detect the real and im-

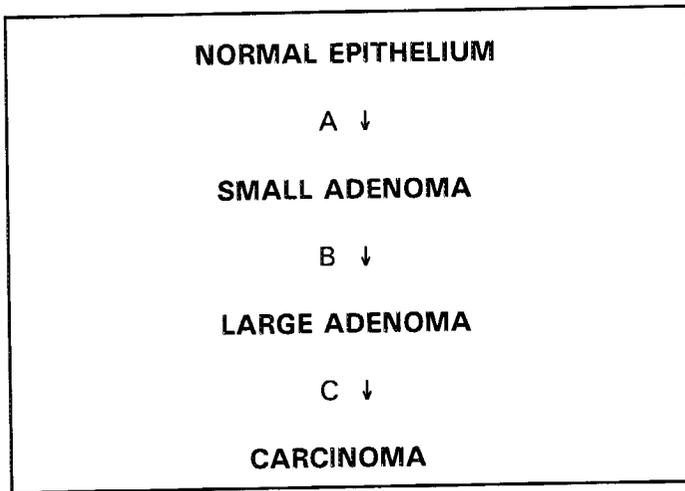


Fig. 3. Model of progression from normal epithelium to adenoma to carcinoma. A = agent causing adenomas to form; B = agent causing adenomas to grow; C = agent causing adenomas to develop into carcinomas.

portant influence of the intervention on the later step of neoplasia development. In other words, the intervention could truly work (in the sense of reducing large-bowel cancer) and the trial could miss it.

It follows that it would be unwise to carry out a polyp recurrence trial without prior evidence supporting an intervention effect at step A (normal epithelium→small adenoma). In the case of the Polyp Prevention Trial, there is indeed such evidence. A number of studies (11,12) suggest that dietary factors can modulate epithelial cell hyperproliferation, which may be a necessary precursor to the formation of small polyps. Several epidemiologic studies (13-18) implicate dietary factors (including fat, fiber, and vegetable consumption) in the etiology of adenoma formation. The large majority of adenomas in these studies were small (<1 cm). In the Health Professionals Study by Giovannucci et al. (15), for example, 73% of the confirmed adenomas were smaller than 1 cm; in the case-control study by Macquart-Moulin et al. (14), two thirds of the polyps were smaller than 1 cm.

Dietary intervention might also operate at the later stages of neoplasia development, but that is not testable when there is a policy to excise all small adenomas. It would be possible to study later-stage effects if clinical policy were to monitor but not excise small adenomas. Such a study is currently being conducted in Europe by the European Cancer Prevention Organization.

Although the intervention might affect the development of small adenomas, alternative inference #3 suggests that this step might occur too infrequently for the relatively short active intervention to demonstrate a positive result. An intervention of greater duration would allow the development of enough small polyps for the protective effect of the intervention to become apparent.

With regard to alternative inference #4, it is biologically plausible that an early event in the carcinogenic process might precede small adenoma formation by at least several years. The successful interruption of this early event by an intervention might not be manifest as reduced adenoma recurrence until

several years or more after base line; at 4 years, however, no intervention effect would be evident. Note that longer follow-up can include a greater duration of intervention, an expanded period of postintervention follow-up, or both. Even if intervention were to cease after 4 years, a positive trial result might become apparent later due to the biologic effect that occurred during the period of active intervention.

It is possible, as reflected in alternative inference #5, that the intervention reduces the subsequent development of bad adenomas only when administered in early life (well before the development of the initial adenoma). In the absence of such an intervention (dietary change, for example), the large-bowel mucosa becomes set in a biologic state that predisposes it to subsequent malignant transformation. That is, there is a point of no return after which the intervention has no effect. Before undertaking a polyp trial in middle-aged and older adults, investigators should have reasonably strong evidence [such as that from migration studies (19)] that the intervention can be effective when implemented in these age groups.

Alternative inferences #1 and #2 for a null trial result are specific to studies with polyp end points. Alternative inferences #3, #4, and #5, however, are also germane to studies with cancer end points.

Polyp Trials: Restricted to Persons With Large Adenomas?

Atkin et al. (20) observed large-bowel cancer incidence in persons with initial adenomas of varying sizes, numbers, and histologic characteristics. They concluded that persons with adenomas 1 cm or larger in diameter or with villous or tubulovillous features had an elevated risk of large-bowel cancer, whereas those with small tubular adenomas had no increased risk. The question that immediately arises is whether trials that randomly assign substantial numbers of persons with small tubular adenoma index lesions will tell us anything about large-bowel cancer if these polyps have no malignant potential.

We do not think that the innocence of all small tubular adenomas (meaning no increased risk of malignancy) has been firmly established. The findings by Atkin et al. (20) need to be confirmed in other studies, particularly in those with a greater number of cancer end points and internal controls rather than external (expected population) comparison rates. The results from the Atkin et al. study are consistent with as much as a 30% increase in the risk of large-bowel cancer in persons with small tubular lesions. Moreover, it is indisputable that large adenomas begin as small ones; some small adenomas, therefore, must have malignant potential.

Because of the short interval between colonoscopies, virtually all recurrent adenomas in polyp trials are small, irrespective of the size of the index lesion. It is conceivable that a greater proportion of recurrent small adenomas in trial participants with large, as opposed to small, index lesions have malignant potential. Nevertheless, a substantial majority of recurrent adenomas in individuals with large-index lesions do not progress to cancer. Therefore, restricting polyp trials to persons with large-index lesions would not overcome the inferential limitations of a posi-

tive study result but would expand the accrual effort considerably and thereby increase the expense of the study.

Conclusion

Factors that decrease adenoma recurrence very likely—but not necessarily—reduce large-bowel cancer incidence. In other words, the evidence relating to large-bowel cancer that derives from polyp trials is strong but not conclusive; alternative explanations of both positive and negative findings are difficult to rule out entirely. For this reason, it is important to evaluate the evidence from polyp trials in conjunction with findings from well-designed observational epidemiologic studies of large-bowel malignancy as well as the (rare) trials with cancer as an explicit end point. Many of the arguments made here with respect to polyp trials apply also to observational epidemiologic studies of adenomas and investigations of other cancer precursor lesions such as cervical intraepithelial neoplasia (21).

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Note

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