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Meta-analysis of Dietary Restriction during Fecal Occult Blood Testing

CONTEXT. Dietary restriction is often recommended during fecal occult blood testing (FOBT) as a means of increasing test accuracy, but concern surrounds whether such restriction also reduces the chance that patients will complete the test.

PURPOSE. We conducted a systematic review and meta-analysis to determine if advice about dietary restrictions affects the rate of completion of FOBT and the rate of positive results.

METHODS. We searched the MEDLINE database and hand-searched the bibliographies of other systematic reviews and clinical practice guidelines to identify randomized trials of advice to perform dietary restriction during FOBT. We included only trials that reported the proportion of patients who completed the occult blood tests (completion rate). When such information was available, we also recorded the proportion of patients who had positive test results (positivity rate).

RESULTS. Five randomized trials met our inclusion criteria. All used guaiac-based Hemoccult tests; none reported results from rehydrated test slides. In four trials, there was little or no difference in test completion between patients assigned to dietary restriction and those with no restriction. In one small trial that used an especially restrictive diet, completion was 21 percentage points lower in the restricted group. Positivity rates were reported in four trials, none of which found a statistically significant difference between groups. Meta-analysis showed no difference in the summary positivity rate between those assigned to dietary restriction versus those not restricted (difference in positivity rate, 0%; 95% CI, -1% to 1%).

CONCLUSIONS. Available data suggest that advice to perform modest dietary restriction during unrehydrated FOBT does not affect the completion rate, but more severe restrictions may. Dietary restriction also does not appear to affect positivity rates. On the basis of these data, physicians do not need to advise patients to restrict their diet for nonrehydrated FOBTs.

Screening for colorectal cancer with fecal occult blood testing (FOBT) has been shown to reduce disease-specific mortality in men and women over age 50 and is recommended by all major clinical practice guidelines.¹⁻² Despite its demonstrated effectiveness, however, FOBT remains underutilized. Recent reports indicate that only 20% to 25% of U.S. adults older than 50 have had FOBT within the past year.³⁻⁴ Many studies have examined barriers to FOBT, and some have found that patients report difficulty in preparing for or performing the test.⁵

One potential barrier to successful test performance is the use of dietary restrictions. Test performance guidelines usually recommend abstinence from certain foods or medicines believed to cause false-positive or false-negative results. For example, the manufacturers of Hemoccult II (Beckman Coulter, Palo Alto, CA) recommend avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, for 7 days

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TABLE 1

Proposed Effects of Dietary and Medication Restrictions during FOBT with Guaiac-Based Tests*

DIETARY OR MEDICATION RESTRICTION	MECHANISM
Maneuvers to decrease false-positive results	
Avoid NSAIDs (including aspirin) for 7 days before and during testing†	NSAIDs may cause gastrointestinal bleeding
Avoid red meat for 3 days before and during testing	Animal heme may cross-react
Avoid peroxidase-containing vegetables for 3 days before and during testing	Vegetable peroxidases can mimic pseudoperoxidase activity of heme
Maneuvers to decrease false-negative results	
Avoid vitamin C for 3 days before and during testing	Vitamin C can block the pseudoperoxidase activity of heme

*Data from Ransohoff and Lang.¹¹ NSAIDs = nonsteroidal anti-inflammatory drugs.

†Evidence suggests that low doses of aspirin do not increase false-positive results, but high doses can. No good data exist for other NSAIDs.

before and during testing. Avoidance of vitamin C (over 250 mg/d), red meat, and raw fruits and vegetables is recommended for 72 hours before and during testing. The rationale for these restrictions is shown in **Table 1**.

Dietary restriction was first recommended by Gregor⁶ on the basis of observations that it decreased positive results. In 1982, Macrae and St. John⁷ found that restricting red meat and “certain other high peroxidase foods” reduced false-positive tests during “rehydrated” FOBT (rehydration is the addition of distilled water to the samples just before development of the slides) but did not affect unrehydrated tests. The practice of dietary restriction, however, has since been widely adopted regardless of rehydration status. **Table 2** details how the three large randomized trials of FOBT addressed the issue of dietary restriction.^{8–10} Despite the widespread recommendation of dietary restriction when performing FOBT, it is unclear whether restriction of certain food items or medicines produces clinically important differences in test accuracy and whether it adversely affects the likelihood that patients will complete the testing.¹¹ It is also ambiguous which foods or medicines should be stopped. These issues need to be clarified to minimize barriers to widespread use of FOBT.

To better understand the effect of dietary restriction on test completion rates (i.e., what proportion of patients completed the occult blood testing), we performed a systematic review of randomized trials of advice to perform dietary restriction during FOBT.

TABLE 2

Dietary and Medication Restriction in Three Large Randomized Trials Examining the Effect of FOBT on Colorectal Cancer Mortality

REFERENCE	DIETARY/MEDICATION RESTRICTION IN FOBT GROUP	HYDRATION	POSITIVITY RATE	COMPLETION RATE*
Kronborg et al ⁸	No red meat, fresh fruit, iron preparations, vitamin C, aspirin, or other nonsteroidal antirheumatic drugs for 3 days before sample collection.	No	1.0%	63%
Mandel et al ⁹	No red meat, poultry, fish, or certain raw vegetables and fruits. No vitamin C tablets or aspirin for 24 hours before and during sample collection.	Yes (80%)†	2.4% unhydrated 9.8% rehydrated	90%
Hardcastle et al ¹⁰	No dietary restriction on initial testing but patients testing positive on 4 or fewer test windows were asked to repeat the test with restrictions (specific restrictions not given). If negative on repeated testing, the test was done again with diet restrictions in 3 months.	No	2.1%	60%

*For the first round of testing.

†An approximate number. Slides were not always rehydrated at the beginning of the study.

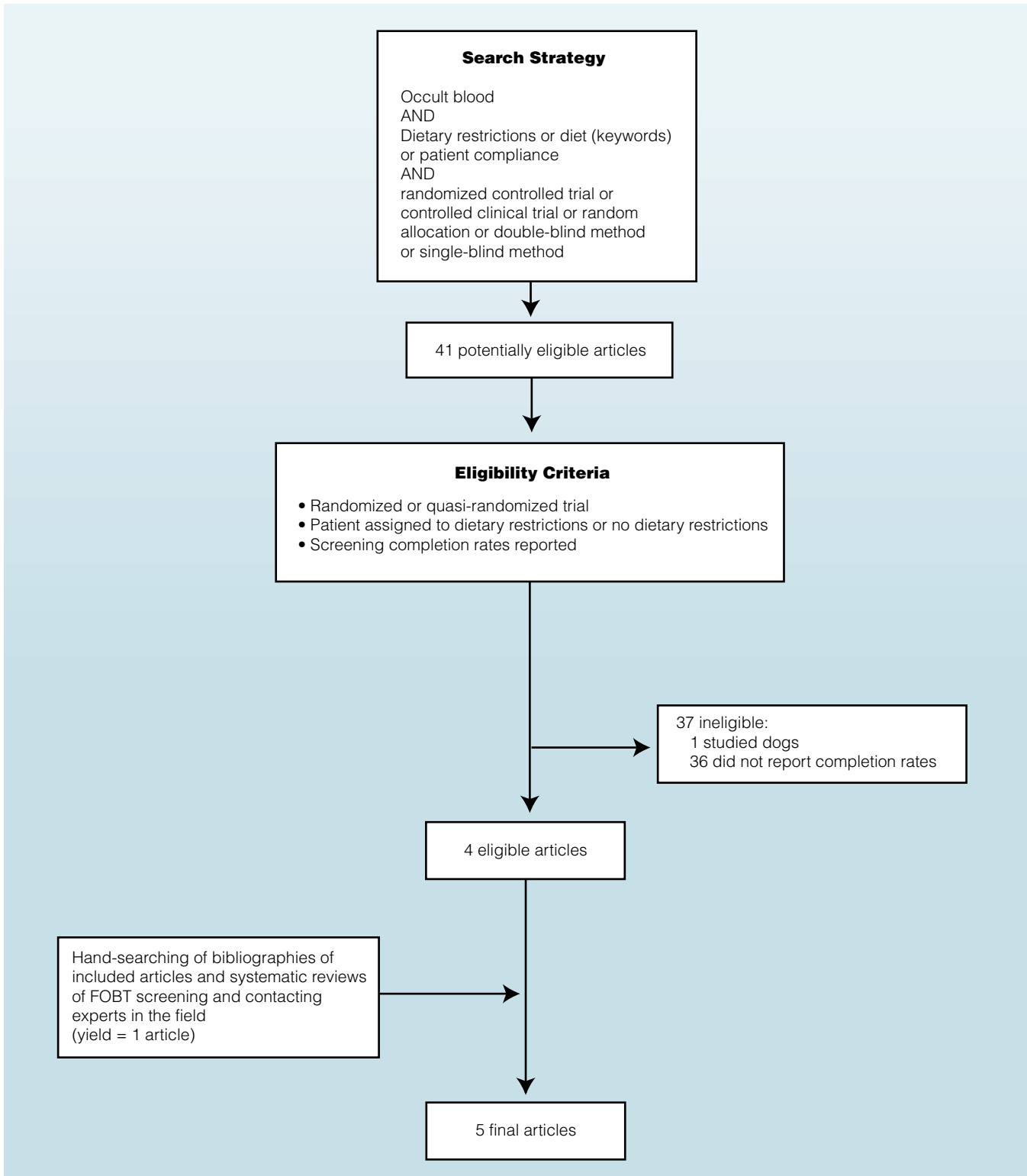


FIGURE 1. Identification of articles for the systematic review.

Methods

Figure 1 shows our literature search, using the MEDLINE database from 1966 to December 1999 and the Medical Subject Headings *occult blood* and *patient com-*

pliance and the key words *diet* and *dietary restriction*. We combined these terms with a validated search strategy for capturing randomized trials to identify abstracts of articles potentially relevant to our question.¹² We also hand-searched the bibliographies of other systematic

reviews and clinical practice guidelines to identify articles possibly missed by our initial search.

We defined eligible studies as those that assigned patients to dietary restriction versus no dietary restriction, reported completion rates, and used a randomized or quasi-randomized design.

Our initial search identified 41 potentially relevant abstracts. Two authors (MP and CC) independently examined the abstracts to identify eligible studies. We reviewed the full articles of abstracts that were identified by either author as possibly relevant. Studies in which patients were randomized to dietary restriction or no restriction and that reported screening completion rates were included. Where there was disagreement between the initial reviewers, a third author (MKC) also examined the abstract or article and consensus was reached by discussion. After initial review, four articles from the main search were found to meet our eligibility criteria. Hand-searching identified one other eligible article. Our final article set included five randomized trials that examined the question of whether recommending dietary restriction affects the rate of completion of FOBT.

Information on the setting, patients, intervention, and completion rates were abstracted from each article and placed in an evidence table. If available, data on positivity rates, defined as the proportion of screened patients who tested positive on FOBT in each group, were also included. For studies that did not report confidence intervals, we calculated them ourselves using the data provided in the articles.

Heterogeneity of results across studies was examined using the Mantel–Haenszel estimation method. Positivity rates were not heterogeneous; we therefore performed meta-analysis using the DerSimonian and Laird random-effects model. We report the absolute difference in positivity rates with 95% CIs using EasyMA software (Department of Clinical Pharmacology, University of Lyon).

Results

Description of the Trials

The five trials studied different populations of patients and advised different levels of dietary restriction during FOBT screening. We describe them briefly here to help the reader assess their validity for answering our main questions and to determine how well they can be generalized to typical outpatient settings in the United States. The main findings are also summarized in **Table 3**. All studies used Hemoccult or Hemoccult II, and none reported performing rehydration.

As part of a larger trial conducted by the American Cancer Society, Elwood and colleagues¹³ studied 3783

American Association of Retired Persons members who were randomized to receive an invitation to perform FOBT with or without dietary advice by mail ($n = 2032$) or at a group meeting ($n = 1751$). All participants were asked to eat a high-roughage diet, and the 1805 patients randomized to dietary restriction were asked to abstain from red meat. The completion rate was slightly lower in the group with dietary restriction than in the unrestricted group (18.1% vs. 20.9%; difference, 2.8%; 95% CI, 0% to 5%). No data on positivity rates were provided.

Hoogewerf and coworkers¹⁴ randomized 32 Canadian family physicians to advise their patients to restrict red meat consumption when performing the FOBT or to give no advice. Both groups were asked to advise their patients to avoid vitamin C and aspirin. They studied 5003 patients presenting for usual care. No time limit for return of the FOBT was reported. They found no difference in return rate with restriction of red meat compared with no restriction (71.6% vs. 70.5%; difference, -1.1%; CI, -3.5% to 1.5%). They also found no difference in positivity rates (2.2 vs. 2.1%; difference, -0.1%; CI, -1.1% to 0.8%).

Joseph¹⁵ assigned 786 patients from a VA hospital to receive advice to restrict their diet or no advice. The outcome of interest was whether the patient returned the FOBT cards within 30 days. The patients in the diet group were also telephoned to assess their adherence to the diet advice; 83% reported adherence to the restricted diet. The FOBT Hemoccult II slides were developed without rehydration. Joseph found no difference in the rate of return with dietary restriction, which included avoiding rare meat, turnips, horseradish, aspirin, and vitamin C for 48 hours before testing (80.4% with restriction vs. 82.2% without restriction; difference, 1.8%; CI, -3.6% to 7.3%). They also found no difference in positivity rates (5.4% vs. 5.6%; difference, 0.2%; CI -3.4% to 3.7%). Based on the results of subsequent evaluations to determine the true state, Joseph found that the proportions of false-positive results (defined as having had a positive FOBT in the absence of neoplasm or other clear source of gastrointestinal bleeding on colonoscopy) were also similar between the groups.

Verne and coworkers¹⁶ randomized patients aged 40 to 74 to dietary restriction (avoidance of red meat, dark fish, and certain vegetables) or no dietary restriction and tested three different occult blood tests. For the 634 participants assigned to Hemoccult testing, they found only a small difference in completion rates: 45.8% with restriction versus 52.0% without restriction (difference, 6.2%; CI, -1.6% to 13.9%). The positivity rates reported in the article were incorrect. Based on our recalculation, the positivity rate was 2.2% with dietary restriction and 5.8% without restriction (difference, 3.6%; CI, -0.6% to 7.9%).

TABLE 3

Randomized Trials of Diet Restriction during FOBT

REFERENCE/TEST	ADVICE TO DIET-RESTRICTED GROUP (ADDITIONAL DIET ADVICE TO BOTH GROUPS)	COMPLETION RATE		DIFFERENCE (95% CI)	POSITIVITY RATE		DIFFERENCE (95% CI)
		WITHOUT DIETARY RESTRICTION	WITH DIETARY RESTRICTION		WITHOUT DIETARY RESTRICTION	WITH DIETARY RESTRICTION	
Elwood et al ¹³ Hemocult (n = 3783)	Meat-free for 24 hours before and during testing (high-roughage diet)	20.9% (413/1978)	18.1% (327/1805)	2.8% (0 to 5%)	NR	NR	NR
Hoogewerf et al ¹⁴ Hemocult II (n = 5003)	No red meat during testing (high fiber; no vitamin C or aspirin)	70.5% (1805/2559)	71.6% (1749/2444)	-1.1% (-3.5% to 1.5%)	2.1% (37/1805)	2.2% (38/1749)	-0.1% (-1.1% to 0.8%)
Joseph ¹⁵ Hemocult II (n = 786)	No rare meat, turnips, horseradish, aspirin, or vitamin C for 48 hours before testing (no additional advice)	82.2% (324/394)	80.4% [†] (315/392)	1.8% (-3.6% to 7.3%)	5.6% (18/324)	5.4%* (17/315)	0.2% (-3.4% to 3.7%)
Verne et al ¹⁶ Hemocult (n = 634)	No red meat, dark fish, or "certain vegetables" for 2 days before and during testing (no additional advice)	52% (173/333)	45.8% (138/301)	6.2% (-1.6% to 13.9%)	5.8% (10/173)	2.2% (3/138)	3.6% (-0.6% to 7.9%)
Robinson et al ¹⁷ Hemocult (n = 153)	No red meat, dark fish, black pudding, tomatoes, cauliflower, parsnips, turnips, radishes, bananas, or broccoli for 2 days before and during testing (no additional advice)	72.7% (56/77)	51.3% (39/76)	21.4% (6.4% to 36.4%)	5.4% (3/56)	7.7% (3/39)	-2.3% (-12.6% to 7.9%)

*Based on the results of subsequent tests to evaluate the true state, the proportion of false-positive results did not differ between groups. NR = no restriction.

[†]Eighty-three percent reported adherence with dietary advice.

Robinson and coworkers¹⁷ randomized 153 British patients from a single general practice to receive FOBT with dietary restriction ($n = 76$) or no dietary restriction ($n = 77$). The restrictions were more stringent than the other trials reviewed here (Table 3). These researchers found large differences in completion rates between patients assigned to dietary restriction and those allowed to eat an unrestricted diet. These differences were present in the initial return rate (27.6% vs. 53.2%) and in the rate after a reminder letter (51.3 vs. 72.7%; difference, 21.4%; CI, 6.4% to 36.4%). The positivity rate was actually higher in the restricted diet group than in the unrestricted group (7.7% vs. 5.4%; difference, -2.3%; CI, -12.6% to 7.9%).

Meta-analysis

To increase the precision of our results, we considered performing meta-analysis of the five eligible trials. For the outcome of test completion, we identified significant heterogeneity among the studies, a consequence of the large difference in completion rates in Robinson's trial. Because of this heterogeneity, we decided against presenting pooled results. There was no evidence of heterogeneity for the positivity rates ($P = 0.39$). For the effect of advice to perform dietary restriction on FOBT positivity rates, our pooled results (Figure 2) show that positivity was not affected by dietary restriction (pooled difference in positivity rate, 0%; CI, -1% to 1%).

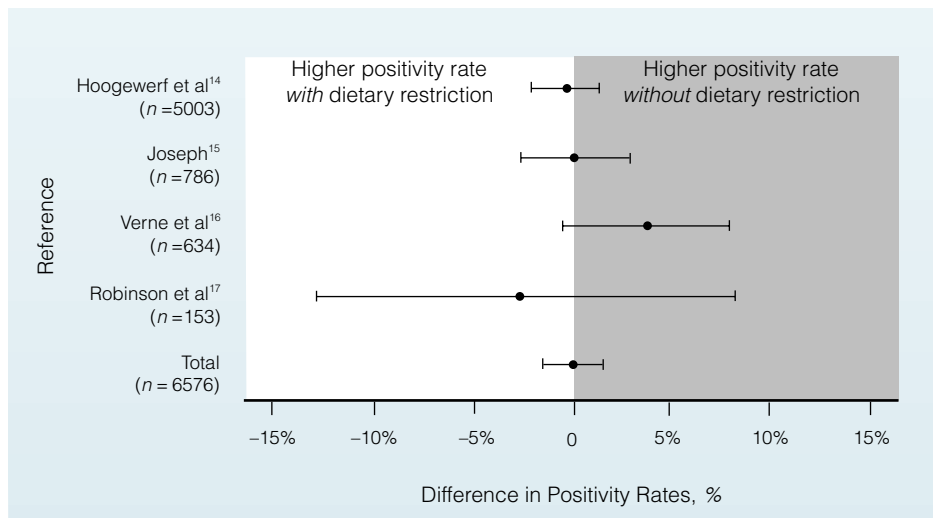


FIGURE 2. Meta-analysis of the effect of dietary restriction on positivity rates for fecal occult blood testing. The pooled difference in positivity rate was 0% (95% CI, -1% to 1%).

Discussion

Many surveys and retrospective analyses suggest that dietary restriction may be a major barrier to completion of FOBT screening. Providers often perceive that patients find FOBT embarrassing, unpleasant, or inconvenient.^{5,18} Our systematic review found that advice to patients to restrict their diet and avoid NSAIDs and vitamin C does not substantially reduce completion of FOBT, except perhaps when the dietary restriction is particularly extensive (as in the study by Robinson and colleagues).

Diet restriction during testing also does not appear to change positivity rates. This finding was consistent among all studies, regardless of the intensity of the restriction. However, because a difference in the positivity rate is not a perfect indicator of differences in false-positive results, we cannot be completely sure that dietary restriction does not improve FOBT accuracy slightly. In addition, because existing trials were unable to directly measure the effect of dietary restriction on sensitivity, we also cannot determine whether restricting vitamin C leads to fewer false-negative results.

The five trials included in our review were well-designed, randomized or quasi-randomized trials that were performed in settings that seem applicable to general primary care in the United States. This increases our confidence that their results are valid. Although others have commented on the small effect of dietary restriction on FOBT completion and positivity,^{5,11} ours is the first review to systematically identify and quantify these effects.

Because all of the studies used unhydrated Hemoccult, we cannot determine if our conclusions, particularly those regarding the effect on test positivity rates, apply to other occult blood tests or to rehydrated Hemoccult. Verne and coworkers¹⁶ found similar completion rates with two “magic toilet paper” tests but found larger differences in positivity rates.

Rozen and colleagues¹⁹ recently studied a newer test, Hemoccult Sensa. They assigned half of the patients in a program of ongoing surveillance to dietary restriction before performing the test and compared their results with those from the other half, which was not given dietary restrictions. They also held the test kits for 3 to 14 days to allow for the breakdown of vegetable peroxidases, the putative source of false-positive results when diet is not restricted. Positivity rates were actually higher in the group that had dietary restrictions (7.2%) than in the group with no dietary restrictions (5.5%), although the result was not statistically significant ($P > 0.2$).

One limitation of the data is that most of the trials did not directly assess the actual degree of dietary adherence. The lack of difference in positivity rates seen in these trials could have occurred because the patients assigned to the dietary restriction group did not comply with the restrictions. However, in the one trial that attempted to measure whether participants followed the restrictions, 83% of intervention patients reported doing so.¹⁵ In addition, because adherence to interventions is usually better in trials than in actual practice, it is unlikely that the differences in positivity rates would occur in the real-world settings if they did not occur in the trials.

Another potential limitation of our review is the small number of studies. We did not formally assess the possibility of publication bias. However, since publication bias usually results from failure to publish small negative studies and the existing trials examined a large number of total participants, it is unlikely that unpublished results would change the primary findings.

Conclusion

Our systematic review and meta-analysis suggest that mild-to-moderate dietary restriction is not a major bar-

rier to completion of occult blood testing for colorectal cancer. However, dietary restriction also does not seem to be an especially strong means of preventing false-positive results during unrehydrated testing. On the basis of these data, providers may decide not to advise dietary restriction during unrehydrated FOBT. However, because we are unsure of the effects of vitamin C on false-negative results, providers may still wish to discourage intake of vitamin C for 3 days before and during testing.

Take-Home Points

- **Dietary restriction during fecal occult blood testing is recommended frequently, but its effect on screening completion rates and impact on test accuracy have not been well assessed.**
- **Our systematic review of randomized trials has shown that completion rates do not differ when modest dietary restrictions are recommended, but more severe restrictions may reduce them.**
- **Positivity rates (an imperfect surrogate for test accuracy) do not seem to be affected by dietary restriction during unrehydrated FOBT.**
- **Because the impact on test accuracy is likely to be small, providers do not need to impose dietary restriction during unrehydrated FOBT. Removal of dietary restriction may reduce real and imagined barriers to screening.**

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