Chapter 3. Results

Description of the Evidence

We accepted from the screening process and submitted for further analysis 36 articles, which represented results from 38 studies on 23 unique trials. From the outcomes of the 38 studies, we found that 21 reported death as a primary outcome; 16 reported on new tumor development; eight focused on the development of colonic polyps; and seven reported on a variety of intermediate outcomes. An individual study may have contributed to more than one analysis, and seven studies reported only on intermediate, not primary, outcomes. Further, ten of these studies were from a large trial, Alpha-Tocopherol Beta Carotene Trial (ATBC), which evaluated the effects of antioxidant supplementation on Finnish, male, smokers. Seven were from 2 large multicenter intervention trials conducted in Linxian, China, focusing on the development of esophageal or gastric cancer in either a general population trial or a second trial in a high-risk population that already had dysplasia. All three large trials were primary prevention studies. All studies used interventions including vitamins C and E; no studies testing the use of coenzyme Q10 went on for further analysis based on study design (i.e. no controlled clinical trials).

The ATBC pilot trial scored five on the Jadad scale, but the intervention trial that followed scored three on the Jadad scale. (Please refer to the Methodology section for a description of the Jadad scale scoring system.) The Linxian Trials scored two for both the Dysplasia and for the General Population Trials. For the smaller trials reviewed, the frequency of Jadad scores was as follows: one trial scored zero; one trial scored one; five trials scored two; three trials scored three; seven trials scored four; and two had a score of five on the Jadad scale.[14]

Analysis of Studies Reporting on Death

Twenty-one studies corresponding to ten trials reported on the outcome of cancer-related death and were considered for a risk ratio analysis. These 21 studies were contained in 19 articles.[11, 12, 23-38] Nine of these studies corresponding to seven articles were excluded for lack of sufficient information on outcome or insufficient statistics and thus were dropped from the analysis. For studies that only reported survival curves it was not possible to derive a risk ratio for death. From an article on a pilot study of the ATBC trial,[23] we were unable to determine if the subjects of the pilot were included in the reports of the larger ATBC study. Thus, this study was not included in the analysis to avoid duplication of data and because, in addition, it had inadequate statistics for analysis. From the Linxian nutritional intervention trials, four studies reported in two articles[11, 12] on either total death or total cancer death and did not separate the results by treatment arm. Three studies evaluated the effect of high-dose vitamin C on advanced cancer. Two of these[27, 33] reported on survival times and did not provide sufficient detail on the number of deaths in each comparison group for our analysis; and the third study[28] had insufficient statistics for analysis. The Moertel study[33] also reported on death as well as survival time but reported on total death, not separated by treatment arm. A final study by Gogos et al,[29] evaluating the effects of omega-3 fatty acids and vitamin E on survival of severely ill cancer patients, only reported on survival times. Therefore, due to inappropriate outcomes or

insufficient statistics, these studies were not included in this analysis. They will be discussed in more detail at the end of this section. In summary, six trials were included in the analysis.

Studies Reporting on Death from the ATBC Trial

The ATBC trial randomized 29,133 male smokers from Finland to receive one of four possible regimens: placebo, alpha-tocopherol alone (AT) (50 mg/day), beta-carotene (BC) alone (20 mg/day), or both vitamins. Patients were followed for a minimum of 5 years and a maximum of 8 years. Six studies from the ATBC trial reported on death due to a variety of different cancer types and reported sufficient data for analysis. Some, in addition, reported on all-cause mortality or all cancer mortality. Results from this analysis are included in Table 4. Please note that the results of the ATBC trial are reported in two different ways in Table 4.

Two studies looked at mortality from lung cancer but reported on this outcome in slightly different ways. Albanes et al[24] reported on death from lung cancer in each of the four treatment arms. The risk ratio (RR) for AT only versus placebo was 0.93 (95% CI: 0.48, 2.47) and for AT combined with BC was 1.15 (95% CI: 0.91, 1.45). The second study[39] combined arms so that results were reported as all arms using AT versus arms without AT. For all-cause mortality, the RR was 1.02 (95% CI: 0.96, 1.08) and for lung cancer death the RR was 1.02 (95% CI: 0.87, 1.2).

Three additional studies reported on death from a variety of other tumor types by individual treatment arms. Heinonen and colleagues[30] reported on the mortality from prostate cancer. For AT versus placebo, the RR was 0.61 (95% CI: 0.29, 1.29), and for AT + BC versus placebo the RR was 0.67 (95% CI: 0.32, 1.38). In an article by Virtamo et al,[38] deaths from urinary tract cancers were reported. For urothelial cell carcinoma, the RR of the AT versus placebo comparison was 1.20 (95% CI: 0.37, 3.93) and for AT + BC versus placebo comparison was 1.6 (95% CI: 0.52, 4.89). For renal cell carcinoma, the RR's were 0.79 (95% CI: 0.36, 1.73) and 0.72 (95% CI: 0.32, 1.61), respectively. Albanes[25] discussed deaths due to colorectal cancer. The RR for AT versus placebo was 1.09 (95% CI: 0.48, 2.47) and for AT + BC versus placebo was 1.18 (95% CI: 0.53, 2.64).

We calculated an RR for a combined death outcome, regardless of tumor type, for the four ATBC studies that reported their results for all four arms (this is not a meta-analysis because results are not pooled across trials).[24, 25, 30, 38] The RR for this combined outcome for AT versus placebo was 0.91 (95% CI: 0.74, 1.12) and for AT + BC versus placebo was 1.08 (95% CI: 0.89, 1.32).

Finally, a single additional study,[37] which reported on mortality from pancreatic cancer, combined the treatment arms and reported all interventions with AT versus all interventions without AT. The RR for this comparison was 1.44 (95% CI: 0.93, 2.23).

Studies Reporting on Death from the Linxian Trials

The first Linxian Nutrition Intervention trial enrolled approximately 30,000 members of the general population of an area of central China that had a very high incidence of carcinoma of the esophagus and stomach. These patients (the General Population Group) were randomized to receive one of eight treatments. They were given either placebo, or formula A (retinol (5000 IU) and zinc oxide (22.5 mg)), or formula B (riboflavin (3.2 mg) and niacin (40 mg)), or formula C (ascorbic acid (120 mg) and molybdenum (30 µg)), or formula D (selenium (50 µg), and beta-carotene (15 mg), and alpha-tocopherol (30 mg)). These formulas were each given in combination with one of the other formulas and all four formulas were given together. No formula was given by itself alone. Interventions using formula C (containing vitamin C) in any combination and interventions using formula D (containing vitamin E) in any combination versus placebo are the comparisons of interest for this report. From the larger population, an additional population, already at higher risk of developing upper gastrointestinal tract cancers due to prior existence of dysplasia of the stomach and/or esophagus, was segregated for a separate trial. They were randomized to receive either a complex intervention—including beta-carotene (15 mg), vitamin A (10,000 IU), vitamin E (60 IU), vitamin C (180 mg), and multiple minerals daily—or placebo.[32] This trial is referred to in the published literature as the Dysplasia Group. Patients were followed for 72 months in both the general study and the dysplasia study.

Two studies from the Linxian Trials had adequate statistics for further analysis. Blot et al[40] report a RR for all-cause mortality in the general Linxian population for any group that took formula C (RR = 1.02 (95% CI: 0.93, 1.1) and formula D (RR = 0.91 (95% CI: 0.84, 0.99)).

Specifically for death due to cancer, the RR for formula C versus placebo was 1.06 (95% CI: 0.92, 1.21) and for formula D versus placebo was 0.87 (95% CI: 0.76, 1.00). This study also reported each of the combination arms individually. No comparison reported a statistically significant benefit. The lowest risk ratio reported for an individual arm was found in the Blot[40] study in the A+D arm (cancer death RR = 0.75 (0.57, 1.00)).

Li and colleagues32 reported on the effect of the supplement intervention in the Dysplasia Group. The intervention was a combination of vitamins including both vitamins C and E. All-cause mortality had a RR of 0.94 (95% CI: 0.77, 1.16). All death due to all cancer had a RR of 0.98 (95% CI: 0.74, 1.31) and for death specifically due to esophageal cancer, the RR was 0.87 (95% CI: 0.56, 1.33).

Studies Reporting on Death from Trials Using Vitamin C as Treatment

Four studies, corresponding to four trials that tested the efficacy of vitamin C for treatment of patients with cancer, had sufficient statistics to proceed for further analysis. However, these trials were not pooled due to the heterogeneous nature of their populations and interventions.

Lamm et al[31] evaluated the effect on patients with transitional cell carcinoma of the bladder of intravesicular and/or percutaneously administered bacillus Calmetee-Guerin (BCG), a substance used to provoke an immune response, combined with either the recommended daily allowance (RDA) of a number of vitamins or a dose of the same supplements which exceeded the RDA (referred to by the authors as megadose). The daily RDA dosage included vitamin A (5,000 IU), vitamin C (60 mg), and vitamin E (30 IU), as well as other vitamins. The megadose intervention included an 800% increase in vitamin A (40,000 IU), and a 3,300% increase in vitamin C (2,000 mg), a 1,330% increase in vitamin E (400 IU) per day, as well as similar increases in other vitamins. The RR comparing the effect of RDA doses of vitamins to the megadoses of vitamins for all-cause death was 0.86 (95% CI: 0.37, 2.01). Two studies examined the effect of vitamin C alone on cancer. Investigators attempted to replicated results reported by Linus Pauling[41] for the efficacy of high-dose vitamin C to prolong survival in cancer patients.[35] They randomized patients with advanced carcinoma of the rectum and colon to receive either placebo or ten grams per day of vitamin C by mouth. The RR for all-cause mortality in this trial (vitamin C versus placebo) was 1.04 (95% CI: 0.69, 1.57). Another trial[36] tested the effects of three grams per day of vitamin C or placebo in a group of 27 breast cancer patients who had already received conventional therapy. The risk ratio for all-cause mortality comparing vitamin C versus placebo is 1.52 (95% CI: 0.72, 3.23). A final trial, the Heart Protection Study Collaboration Group,[34] randomly assigned 20, 536 adults (ages 40-80) to receive either antioxidant vitamin supplements (600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) or a placebo. The study was primarily designed to assess cardiovascular endpoints in a high-risk population, however, all cause mortality was reported as well. The RR reported for this study was 1.04 (95% CI: 0.97, 1.11).

Summary of Results from the Analysis of Death

The results of all of the studies included in this analysis are summarized in Table 5. For the interventions tested, in the populations described, there is no evidence for a benefit for survival.

Trials Not Included in the Death Analysis

Nine studies were considered for the preceding analysis because they appeared to report on death, but they then were excluded due to insufficient statistics or other reasons. These studies will be briefly discussed here.

Albanes et al[23] reported on a pilot of the ATBC trial. Although the main focus of the pilot study was to assess enrollment and compliance issues, dropouts due to death or cancer were mentioned. These results were not separated either by outcome or intervention and thus were not amenable to analysis. In addition, it is not clear if these subjects were then included in the main study and had results reported again. This pilot study had a Jadad score of 5.

Two articles, corresponding to four studies from the Linxian General Population and Dysplasia Trials, were excluded. The first[11] represented two studies because it presented the methodology for the General Population Trial as well as the Dysplasia Trial that is described earlier in this section. The results of these pilot studies demonstrated that it was feasible to conduct these trials.

The third and fourth studies reported in the article from the Linxian Trial[12] reported that the total number of deaths for the general and intervention trials combined was 2,100; of those, 37% of the total deaths were due to cancer. In addition, the authors reported that none of the four combination supplements in the General Population Trial produced a significant reduction in the prevalence of death from esophageal, gastric, or other cancer.

Three studies corresponding to three unique trials involving the use of vitamin C from the same research group[27, 28, 33] and one additional study of the efficacy of vitamin E to treat advanced stage cancer[29] were not included in the analysis. These results are described briefly here.

Creagan, Moertel, O'Fallon, and colleagues[27] reported on a randomized, double-blinded trial of 150 patients with proven terminal cancer of a variety of types, all of whom had previously received conventional care, including cytotoxic drugs. The intervention group received high-dose vitamin C (10 g daily), whereas the control group received a placebo. The two groups did not differ significantly in survival (mean survival for both groups was approximately 7 weeks). Because only survival-curve data were provided, it was not possible to include these results in the death risk ratio analysis.

This same research team published an abstract of what appears to be a subset of the previous trial.[42] They had enrolled the first 128 of the expected 160 patients.

Finally, Moertel, Fleming, Creagan, and colleagues[33] conducted a second prospective, randomized, double-blind, controlled trial on the effect of high-dose vitamin C (2500 mg daily) in 100 patients with advanced colorectal cancer. In contrast to the previous study by this group, none of the patients in this trial had received prior treatment with cytotoxic drugs. The patients were followed as long as they could take the oral medications or until there was evidence of marked progression of the malignant disease. They were assessed at 4 weeks and every 8 weeks thereafter. Because only total deaths were reported, the results of the study could not be included in the pooled analysis. The vitamin C therapy showed no advantage over the placebo for either tumor progression or survival, and no patient with measurable disease had objective improvement.

The final treatment trial not included in the analysis was by Gogos et al[29] and focused on the effect of supplementation with omega-3 polyunsaturated fatty acids plus vitamin E on immune parameters in severely ill cancer patients. In a prospective, randomized, controlled study, 60 patients with generalized solid tumors were given either 200 mg of vitamin E daily plus 18 grams of fish oil daily or placebo until their deaths. None of the patients had received chemotherapeutic or immunomodulating agents during the 4 months prior to the study, and none were being treated for their tumors at the time of the study. Because only the survival curve was reported and showed the results could not be pooled in the death analysis.

Analysis of Studies Reporting on New Tumor Development

Sixteen studies, corresponding to 14 articles and four unique trials, were considered for further analysis of the development of new tumors or recurrence of tumors.[11 (Studies A&B), 12 (Study A), 24, 31, 33, 34, 37-40, 43-45] Four studies from the Linxian Trials were excluded for inadequate statistics.[11, 12, 40] The RRs were reported as adjusted risk ratios and insufficient data were given to be able to convert them to unadjusted risk ratios and make the results comparable to those reported for other trials. This study will be discussed briefly at the end of this section.

Studies Reporting on New Tumor Development from the ATBC Trial

Seven studies of the ATBC trial reported on the development of a variety of new tumors. Results of this analysis are summarized in Table 6. Details of the design of the ATBC trial are discussed earlier in the section entitled Studies Reporting on Death from the ATBC trial.

An article by Varis et al[45] reported on the risk of developing carcinoma (all cell types). They analyzed their data separately for each of the four interventions. For developing a new carcinoma, they reported a RR of 1.04 (95% CI: 0.15, 7.32) for the AT versus placebo comparison and 1.84 (95% CI: 0.34, 10.01) for the AT + BC comparison.

Two studies reported on development of new lung carcinomas in the ATBC trial but in slightly different ways. The ATBC study[39] analyzed the results of the ATBC trial by combining all arms that had a particular intervention. Thus, their analysis reported on the relative risk of developing a new lung cancer in groups that did or did not take alpha-tocopherol without separating the AT-only group from the AT + BC group. Additionally, in the BC versus no BC comparison, the BC + AT group and the BC groups are combined. The RR for this study was 0.98 (95% CI: 0.86, 1.11). The second study to look at the development of new lung tumors, reported on in Albanes et al,[24] analyzed each of the four arms separately. They reported a RR for the development of new lung cancers for the AT versus placebo comparison of 0.98 (95% CI: 0.81, 1.19) and for AT + BC of 1.16 (95% CI: 0.96, 1.39).

All of the remainder of the ATBC studies analyzed each of the four intervention arms separately and focused on the development of a variety of different tumor types. Heinonen and colleagues[30] reported on the development of new prostate cancers. For the AT versus placebo comparison, the RR was 0.64 (95% CI: 0.44, 0.94), and for the AT + BC versus placebo comparison, the RR was 0.84 (95% CI: 0.59, 1.19). Virtamo et al[38] assessed the effects of AT and BC on development of urinary tract cancers. For development of urothelial cancers, the AT versus placebo comparison had a RR of 1.27 (95% CI: 0.83, 1.95), and for AT + BC the RR was 1.14 (95% CI: 0.73, 1.77). For development of renal cell cancer, the AT versus placebo comparison had a RR of 1.00 (95% CI: 0.59, 1.70), and for AT + BC, the RR was also 1.00 (95% CI: 0.59, 1.71).

For development of new pancreatic carcinomas, Rautalahti and colleagues[37] analyzed data from each of four arms separately as well as by combining all AT arms together. The RR for the AT versus placebo comparison was 0.96 (95% CI: 0.56, 1.66); for AT + BC versus placebo was 1.00 (95% CI: 0.58,1.72); and for AT versus no AT was 1.34 (95% CI: 0.88, 2.04). Albanes et al[25] reported on the development of new colorectal cancers. The RR for AT versus placebo was 0.78 (95% CI: 0.48, 1.27) and for AT + BC versus placebo was 0.81 (95% CI: 0.50, 1.31).

We combined the tumor outcomes of the five studies that reported on results by separate arms[24, 25, 30, 37, 38] regardless of tumor type (this is not a meta-analysis because results are not pooled across trials). The resulting RR for the AT versus placebo comparison was 0.93 (95% CI: 0.81, 1.07); and for the AT + BC versus placebo, the RR was 1.05 (95% CI: 0.92, 1.20).

Studies Reporting on New Tumor Development from the Linxian Trials

Four studies from the Linxian Trials reported on the outcome of new tumor development. One study[12] reported on the development of new gastric and esophageal cancers in the General Population Trial. Three of these studies[12, 32, 43] reported on similar outcomes from the Dysplasia portion of the Linxian Trial. One of these studies[12] could not be included in the analysis due to insufficient statistics. The details of this analysis are summarized in Table 7. Details of the designs of the Linxian General Population and Dysplasia Group Trials are included in the earlier section entitled Studies Reporting on Death from the Linxian Trials.

Taylor and colleagues[12] did not report directly on new tumors in the entire General Population Trial sample, although they noted that a total of 1,298 incident cancers were identified in this group. Instead, they reported on new tumor development in a subset of the entire General Population Trial sample who received an endoscopy with gastric and esophageal biopsies at the completion of the 5.25-year trial. This intervention was designed to find cancers that had not been identified by usual means during the course of the trial. The RR for presence of an additional new carcinoma on esophageal biopsy for the C versus no C comparison was 1.18 (95% CI: 0.27, 5.20) and for the D versus no D comparison was 0.71 (95% CI: 0.17, 2.95). The RR for the presence of a new tumor on gastric biopsy was 2.71 (95% CI: 0.55, 13.25) for the C versus no C comparison and was 1.22 (95% CI: 0.31, 4.79) for the D versus no D comparison.

Three studies also reported data on new tumor development in the Dysplasia Trial. Taylor and colleagues[12] noted that a total of 448 incident cancers were found in the Dysplasia Trial but did not separate the results by intervention. No additional analysis was performed on this group and the results were not reported in sufficient detail to permit further analysis. Li and colleagues[32] reported risk ratios for the development of either esophageal or gastric cancer after 72 months of treatment. For esophageal cancer the RR was 0.96 (95% CI: 0.76, 1.22); for gastric cancer the RR was 1.19 (95% CI: 0.89, 1.58); and for all cancers combined the RR was 1.03 (95% CI: 0.87, 1.22).

Dawsey and colleagues[43] reported on the results of biopsies done of the gastric and esophageal areas during the Linxian Dysplasia Trial (30 months) and at the end of the trial (6 years). The number of cancers reported is smaller than in the Li[32] study, because this study does not report on all incident cancers identified during the trial, just the cases identified by biopsy.

The RR for the presence of new esophageal tumors during the midpoint of the trial was overall 0.99 (95% CI: 0.60, 1.64); for the esophagus only it was 0.78 (95% CI: 0.41, 1.49); and for the stomach only it was 1.63 (95% CI: 0.75, 3.52). At the completion of the trial, the RR for the overall rate of the presence of a new tumor was 0.92 (95% CI: 0.54, 1.57); for the esophagus alone it was 1.53 (95% CI: 0.51, 4.58); and for the stomach only it was 0.91 (95% CI: 0.49, 1.68).

Studies Reporting on New Tumor Development from Other Trials

Two trials besides the ATBC and Linxian Trials reported on the outcome of new tumor development. Lamm et al[31] was a treatment secondary prevention trial as opposed to a primary prevention trial. It tested the effect of vitamin supplementation on the development of new bladder tumors in patients previously treated for transitional cell carcinoma of the bladder. (The details of this study design are discussed earlier in the section entitled Studies Reporting on Death from Trials Using Vitamin C as Treatment.) Compared to RDA doses of vitamins, megadoses of vitamins were associated with a reduced RR of 0.50 for new bladder tumors (95% CI: 0.32, 0.78). The Heart Protection Study Collaboration Group,[34] randomly assigned 20, 536 adults (ages 40-80) to receive either antioxidant vitamin supplements (600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) or a placebo. The study was primarily designed to assess cardiovascular endpoints in a high-risk population, however, new tumor development was reported as well. The RR reported for this study was 0.98 (95% CI: 0.89, 1.08).

Summary of Results from the Analysis of New Tumor Development Outcome

The results of all of the studies included in this analysis are summarized in Table 7. For the interventions tested, in the populations described, there is no evidence for a benefit for primary prevention of new tumors except for a single arm of the ATBC trial, AT versus placebo for the development of new prostate cancers. The single treatment/secondary prevention trial discussed did report that the addition of megadose vitamins conferred a benefit. However, the ability to generalize from this finding is limited because the intervention was multicomponent, preventing attribution of efficacy to any particular component. Additionally, all groups also received BCG, a major confounder.

Studies Not Included in the New Tumor Development Analysis

Four studies from the Linxian Trial were not included in the new tumor analysis.[11 (Studies A&B), 12 (Study A), 40, 46] Blot's study reported adjusted risk ratios for the development of gastric or esophageal cancer. Insufficient information was given to calculate unadjusted risk ratios; therefore, these data were not included in the previous analysis. However, the adjusted risk ratios for this trial (adjusted for age and sex), reported by individual arm, were for all cancer (C versus no C) 1.06 (95% CI: 0.95, 1.18), and for D versus no D 0.93 (95% CI: 0.83, 1.03). For esophageal cancer (C versus no C), the adjusted RR was 1.06 (95% CI: 0.91, 1.24) and for D versus no D was 1.02 (95% CI: 0.87, 1.19). For gastric cancer, (C versus no C) the adjusted RR was 1.10 (95% CI: 0.92, 1.30) and for D versus no D was 0.84 (95% CI: 0.71, 1.00).

Li and colleagues' article[11] presents the methodology for the Linxian General Population and Dysplasia Trials. These studies and their new tumor results are described in the death analysis. As noted earlier, the study by Taylor[12] on the Linxian Dysplasia Trial could also not be included due to insufficient statistics.

Analysis of Trials Reporting on Development of Colonic Polyps

The presence of adenomatous polyps of the colon is considered a significant risk factor for the development of colon cancer. Thus, interventions that would decrease the rate of polyp formation would be of interest in decreasing the risk of colon cancer. Eight studies corresponding to 8 articles and 7 unique trials reported on the development of adenomatous polyps of the colon and were considered for pooled analysis.[47-54] Two studies by Roncucci[50, 51] corresponded to the same trials and presented duplicate data; therefore, only the first study was included in the analysis. The remaining six studies corresponded to six unique trials.

One trial focused on the primary prevention of new colonic polyps in a general population[52] while two trials[53, 54] considered the effects of an antioxidant intervention on polyp recurrence in patients with familial polyposis, a condition characterized by extensive polyps in the colon and a greatly increased risk of developing colon cancer. Finally, four trials[47-50] evaluated the ability of antioxidants to decrease the recurrence of colonic polyps in nonfamilial polyposis patients with preexisting adenomatous colonic polyps. The four trials that focused on the secondary prevention of recurrent colonic polyps in patients with previous colonic polyps were judged sufficiently homogeneous to attempt a pooled analysis. The results of trials not included in this analysis will be discussed following the next section.

Meta-Analysis for Secondary Prevention of Polyp Formation

Interventions in these four trials varied. There were no trials that used either vitamins C or E as single interventions. All treatment arms were not pooled because it was felt that vitamins C and E, with and without beta-carotene or vitamin A, were not equivalent interventions. Within the groupings of vitamins C and E with and without beta-carotene or vitamin A, there were insufficient studies to perform an analysis stratified based on dosage.

Specifically, the interventions and doses for these trials are herein discussed. Greenberg and his colleagues[47] gave 864 patients either placebo or beta-carotene (25 mg daily) or vitamin C (1 gm daily) and vitamin E (400 mg daily) or all three vitamins in a two-by-two factorial design for 4 years. McKeown-Eyssen et al[49] randomly assigned 200 patients to receive either placebo or vitamin C (400 mg daily) and alpha-tocopherol (400 mg daily) for 2 years. Hofstad and colleagues[48] gave 116 patients either placebo or a mixture of beta-carotene (15 mg), vitamin C (150 mg), vitamin E (75 mg), selenium 101 µg, and calcium (1.6 gm) daily for 3 years. For the trial performed by Roncucci and his colleagues,[50] 225 individuals were given either no treatment or lactulose (20 gm/day) or a combination of vitamin A (30,000 IU), vitamin C (1 gm), and vitamin E (70 mg) per day for an average of 18 months.

Trials Featuring Combinations of Vitamins C and E Only for Secondary Prevention of Polyp Formation

Two trials[47, 49] of the four considered for pooled analysis had treatment arms that involved the combination of vitamins C and E without beta-carotene or vitamin A. Details of these trials are summarized in the Evidence Table. Because there were only two trials, a pooled analysis was not performed. The estimated risk ratios for these two trials, along with their 95% confidence intervals, are summarized in Table 8. A lower RR in this analysis favors treatment because it represents a lower likelihood of forming new colonic polyps as compared to placebo.

The RRs for the Greenberg and the McKeowen-Eyssen trials are not significantly different from 1; therefore there is no evidence that the combinations of vitamins C and E tested are more effective than placebo in the secondary prevention of recurrent adenomatous polyps of the colon.

Trials Featuring Combinations of Vitamins C and E with Beta-Carotene or Vitamin A for Secondary Prevention of Polyp Formation

Three trials of the four considered for pooled analysis used combinations of vitamins C and E with carotenoids compared with a placebo. Two trials were placebo-controlled. Details of these trials are summarized in the Evidence Table. The three interventions were considered sufficiently equivalent to allow pooling—even though calcium, which was included in the intervention used in the Hofstad trial,[48] has activity of its own in prevention of polyp formation, and vitamin A (not beta-carotene) was used in the Roncucci trial. The estimated RRs for these three studies, along with their 95% confidence intervals and the pooled estimate, are summarized in Table 9 and in Figure 2.

The pooled estimate yields a RR of 0.6, which is clinically important but not statistically significant ($p = 0.13$). In addition, the chi-squared test of heterogeneity is significant ($p = 0.001$), indicating a high degree of heterogeneity among these trials. Sensitivity analyses to account for heterogeneity could not be performed due to the small number of trials, but a visual inspection of Figure 2 suggests that heterogeneity may be due to the differences in population size and numbers of outcomes observed between Roncucci[50] versus Greenberg[47] and Hofstad.[48] For example, Hofstad has the smallest total sample size ($n = 93$) but has a number of outcomes that are proportionally greater than either of the other two trials. Conversely, for a relatively large total number of patients ($n = 209$), Roncucci develops many fewer new colonic polyps. It is likely, therefore, that a significant amount of this heterogeneity is due to patient population selection.

Assessing publication bias with so few trials is difficult at best. The funnel plot represented in Figure 3, although limited, shows no obvious bias. In addition, formal statistical tests revealed no statistically significant bias.

Trials Reporting on Polyp Formation Not Included in the Above Analysis

Three trials were not included in the prior analysis.[52-54] The details of these trials are included in the Evidence Table, and their salient features will be briefly discussed here.

The primary prevention trial reported by Malila and colleagues,[52] as part of the ATBC Trial, was not appropriate for pooling with other secondary prevention trials on the grounds of clinical issues and study design. The other 2 trials[53-54] study populations at extraordinarily high risk of developing polyps. They were felt to be clinically dissimilar enough to preclude pooling of their data with populations with average risk. Malila and colleagues evaluated a subgroup (15,538) of the 29,133 male Finnish smokers enrolled in the trial. Subjects who were not known to have colonic polyps at the start of the trial were randomly assigned to one of four groups: vitamin E (50 mg/day, n = 3,890); beta-carotene (20 mg/day, n = 3,883); both supplements (n = 3,878); placebo (n = 3,887). Patients were followed for an average of 6.2 years. Whereas vitamin E supplementation resulted in a statistically significant increase in the risk for development of new adenomas (RR 1.66; 95% CI: 1.19, -2.32), it did not increase the risk for developing colorectal cancer. Beta-carotene had no effect on the risk of developing adenomas (RR 0.97; 95% CI: 0.69, -1.38) or cancer.

Bussey, DeCosse, Deschner, and colleagues[54] reported on a randomized, double-blind trial of 47 patients with polyposis coli, a familial condition that causes extensive polyp formation in the colon and leads to a high risk of cancer formation, who received either vitamin C (3 gm daily) or a placebo. At 21 months, rectal mucosal biopsies were taken from 31 subjects. The results showed a reduction in the polyp area for the vitamin C arm at the 9-month follow-up ($p < 0.03$) and trends toward a reduction in both the number and area of rectal polyps during the middle of the trial.

DeCosse, Miller, and Lesser[53] reported on a randomized, double-blind trial in 58 patients with familial adenomatous polyposis (polyposis coli) who had undergone a total colectomy with ileorectal anastomosis at least 1 year prior to the commencement of the trial and had a residual section of rectum and sigmoid colon (of on average 15 cm) that would be susceptible to new tumor formation. Patients were given either vitamin C (4 gm/day) and vitamin E (400 IU/day) or high-dose fiber (22.5 gm/day), or assigned to a control group that had only low-dose fiber (2.2g/day) plus placebo. The trial lasted 4 years, during which patients received serial proctosigmoidoscopies (total of 18). All new colonic polyps (recurrence) and growth in preexisting colonic polyps (progression) were recorded. The results suggested a limited effect of the supplements on rectal polyp recurrence and progression.

Trials Reporting on Intermediate Outcomes

Seven studies corresponding to seven trials (one of these studies reports on the ATBC trial) reported on a variety of intermediate outcomes relevant to the development of cancer or improvements in the risk factors for development of a particular type of cancer.[55-61]

Two trials evaluated the effects of antioxidants on the development or progression of risk factors for gastric cancer.[56, 62] One of the widely recognized precursors to intestinal gastric carcinoma is chronic atrophic gastritis with intestinal metaplasia. Zullo, Rinaldi, Hassan, and colleagues[56] conducted a randomized, controlled trial using vitamin C in patients with chronic atrophic gastritis. Following eradication of *Helicobacter pylori*, 66 patients with documented metaplasia received either vitamin C (500 mg/day) or no treatment (the method of randomization was not described) for 6 months. At the end of the trial, endoscopic examination demonstrated a significant decrease in the appearance of intestinal metaplasia in the vitamin C group compared with the control group. In addition, among those who presented with chronic inactive pangastritis with widespread metaplasia at entry, less extensive antritis with intestinal metaplasia was seen in the intervention group. The researchers concluded that vitamin C helps resolve intestinal metaplasia and may, by implication, be effective for primary prevention of gastric carcinoma in this high-risk group.

In a trial of patients with two precancerous, multifocal atrophic gastritis and dysplasia,[62] subjects (n = 631 who completed at 72 months) were randomly assigned to one of 8 arms of the study: placebo; anti-*Helicobacter pylori* triple therapy; beta-carotene; vitamin C; anti-*Helicobacter pylori* plus beta-carotene; anti-*Helicobacter pylori* plus vitamin C; beta-carotene plus vitamin C; anti-*Helicobacter pylori*, plus beta-carotene plus vitamin C. The dosage was 30 mg per day for beta-carotene and 1 g twice a day for vitamin C. The anti-*Helicobacter pylori* therapy consisted of amoxicillin (500 mg 3 times daily), metronidazole (375 mg 3 times daily), and bismuth subsalicylate (262 mg 3 times per day). Patients were evaluated at 36 and 72 months. All three basic interventions (H. pylori treatment, beta-carotene, and vitamin C) in this high-risk population resulted in significant increases in the rates of regression. (RRs were 4.8; 5.1, and 5.0, respectively). The authors concluded that all three treatments might interfere with a precancerous process and provide benefit in a high-risk population.

Two trials evaluated the effects of an antioxidant intervention on the development of oral leukoplakia, which is considered to be a risk factor for the development of oral cancer.[55, 63] Smoking increases the occurrence of oral leukoplakia and increases the number of keratinized cells in the epithelium of the tongue and palate, even when the mucosa in these areas is clinically normal. However, the link between these intermediate outcomes and cancer is not as clearly established as the link with other intermediate outcomes such as the presence of adenomatous polyps with adenocarcinoma of the colon. Nevertheless, the ATBC trial by Liede, Hietanen, Saxen, and colleagues[63] studied the impact of vitamin E and beta-carotene on the prevalence of oral mucosal lesions in smokers in a randomized, double-blind study. A random sample of 409 participants in a cancer prevention study (the ATBC study) was chosen to receive supplementation with either vitamin E (50 mg/day), beta-carotene (20 mg/day), or a placebo for 6 years. An oral examination was performed at the end of the trial. No statistically significant differences were found among any of the groups in the prevalence of oral mucosal lesions. In fact, only 24 patients in total had leukoplakia (5.9% of the total population) and only 7 of those 24 lesions were dysplastic.

In a randomized, controlled, double-blind fashion, 532 men between 50 to 69 years of age with oral leukoplakia and/or chronic esophagitis[55] were given either riboflavin, or retinol with beta-carotene and vitamin E, both, or a placebo. A significant reduction in oral leukoplakia was noted after 6 months for those receiving retinol, beta-carotene and vitamin E. After 20 months, no effect was seen in chronic esophagitis—although the risk for progression was lower in the retinol, beta-carotene and vitamin E group. Doses of 100,000 IU of retinol, 80 mg vitamin E, and 80 mg of riboflavin were administered weekly. The complexity of the intervention and difference in response between groups make interpretation of the efficacy of any single item difficult.

A single trial evaluated the effect of an intervention vitamin C with and without beta-carotene, and all groups were compared to placebo in women with cervical abnormalities that, if untreated, may progress to cervical carcinoma.[57] Mackerras et al[57] conducted a randomized double-blind study with a placebo in 141 women with confirmed minor squamous atypia or cervical epithelial neoplasia (CIN) stage I. The subjects were assigned randomly to an oral daily dose of 30 mg beta-carotene or 500 mg vitamin C, both, or neither. Over 2 years of follow-up, there was no statistically significant difference in the regression of the lesions. Therefore, the researchers concluded that high doses of either compound increases the rate of regression or decreases the progression of minor atypia or CIN l. Again, because the outcome measured is not fully developed cancer per se, it was not included in the pooled analysis.

A different intermediate end point was used in the trial by Cahill, O'Sullivan, Mathias, and colleagues.[58] Colonic crypt cell proliferation and a shift in the proliferative zone in the crypt are precursors to colon carcinoma. Following colonoscopy and colon biopsy, ten patients were randomly assigned to each of four intervention arms: arm 1 of the trial received no supplementation, arm 2 received vitamin E (160 mg/day), arm 3 received vitamin C (750 mg/day), and arm 4 received beta-carotene (9 mg/day). Twenty subjects with a normal colonoscopy and normal colonic mucosa were included as a control group. After 1 month, colonic biopsies were repeated. Both vitamin C and beta-carotene significantly reduced the total proliferation, but vitamin E had no effect. Beta-carotene reduced the colonic cell proliferation only at the base of the crypts, whereas vitamin C reduced proliferation in all crypt compartments from the apex to the base, when compared to age- and gender-matched controls.

A rising prostate specific antigen (PSA) level is a widely used diagnostic method for identifying possible presence of early prostate cancer. This is not an intermediate outcome or a risk factor for a particular cancer per se, but it does have interest as a possible way to detect early tumors. The reliability and utility of PSA to screen for prostate cancer is controversial however it is used as a tumor marker in patients who have undergone prostatectomy. In a randomized, double-blinded, crossover, prevention trial, Schroder, Kranse, Dijik, and colleagues[64] examined the impact of a dietary intervention on prostate cancer in a sample of 37 men with rising PSA levels after undergoing radical prostatectomy, radiotherapy, and pelvic node dissection, but no endocrine treatment. The dietary intervention included soy extract, tea extract, carotenoids, phytosterols, selenium, and vitamin E (doses not given) in addition to a regular diet. The effect of the diet on PSA levels was assessed relative to that of a placebo during a two-week run-in period followed by two 6-week crossover periods that alternated with two washout periods. The results showed that during the supplement treatment periods, the slope of the normal rise in PSA

was decreased, which translated into an 8-week delay in the rise of the PSA with a 6-week course of supplements. The effect of such a delay on prostate cancer mortality on other clinical outcomes is not known.

Table 4. Risk Ratios for Death Outcome for ATBC Trial.

Study	Author, Year	Type of death	Intervention	Sample Size	FU Time	# of deaths	RR (95% CI)
ATBC	Albanes, 1996[24]	Lung cancer	AT	7286	6.1 yrs	125	0.93 (0.73, 1.19)
			AT+BC	7278		154	1.15 (0.91, 1.45)
			Placebo	7287		134	
	Heinonen, 1998[30]	Prostate cancer	AT	7286	6.1 yrs	11	0.61 (0.29, 1.29)
			AT+BC	7278		12	0.67 (0.32, 1.38)
			Placebo	7287		18	
	Albanes, 2000[25]	Colorectal cancer	AT	7286	6.1 yrs	12	1.09 (0.48, 2.47)
			AT+BC	7278		13	1.18 (0.53, 2.64)
			Placebo	7287		11	
	Virtamo, 2000[38]	Urothelial cancer	AT	7286	6.1 yrs	6	1.20 (0.37, 3.93)
			AT+BC	7278		8	1.60 (0.52, 4.89)
			Placebo	7287		5	
	Virtamo, 2000[38]	Renal cell cancer	AT	7286	6.1 yrs	11	0.79 (0.36, 1.73)
			AT+BC	7278		10	0.72 (0.32, 1.61)
			Placebo	7287		14	
	Albanes, 1996,[24] 2000[25]; Virtamo, 2000[38]	Combined cancer (lung, colorectal, urothelial, and renal cell)	AT	7286	6.1 yrs	165	0.91 (0.74, 1.12)
			AT+BC	7278		197	1.08 (0.89, 1.32)
			Placebo	7287		182	
	Alpha-Tocopherol, 1994[39]	All cause	AT	14564	6.1 yrs	1798	1.02 (0.96, 1.08)
			no AT	14569		1768	
		Lung cancer	AT	14564	6.1 yrs	285	1.02 (0.87, 1.20)
			no AT	14569		279	
	Rautalahti, 1999[37]	Pancreas cancer	AT	14564	6.1 yrs	49	1.44 (0.93, 2.23)
			no AT	14569		34	

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the Evidence Table.
AT: alpha-tocopherol; BC: beta-carotene; CI: confidence interval; RR: risk ratio

Table 5. Risk Ratios for Death Outcome for Linxian and Other Trials.

Study	Author, Year	Type of death	Intervention	Sample Size	FU Time	# of deaths	RR (95% CI)
Linxian Dysplasia	Li, 1993[32]	All cause	Supplement	1657	6 yrs	157	0.94 (0.77, 1.16)
			Placebo	1661		167	
	Li, 1993[32]	Cancer	Supplement	1657		87	0.98 (0.74, 1.31)
			Placebo	1661		89	
	Li, 1993[32]	Esophageal Cancer	Supplement	1657		38	0.87 (0.56, 1.33)
			Placebo	1661		44	
Linxian General Population	Blot, 1993[40]	All cause	*A+B*	3701	5.25 yrs	265	0.94 (0.80, 1.11)
			A+C	3694		296	1.05 (0.90, 1.23)
			A+D	3703		250	0.89 (0.75, 1.05)
			B+C	3691		268	0.95 (0.81, 1.12)
			B+D	3699		263	0.93 (0.79, 1.10)
			C+D	3705		249	0.88 (0.75, 1.04)
			A+B+C+D	3712		256	0.91 (0.77, 1.07)
			Placebo	3679		280	
			C	14802		1069	1.01 (0.93, 1.10)
			No *C*	14782		1058	
			D	14819		1018	0.91 (0.84, 0.99)
			No *D*	14765		1109	
	Blot, 1993[40]	Cancer death	*A+B*	3701	5.25 yrs	94	0.87 (0.66, 1.15)
			A+C	3694		121	1.13 (0.87, 1.45)
			A+D	3703		81	0.75 (0.57, 1.00)
			B+C	3691		101	0.94 (0.72, 1.23)
			B+D	3699		103	0.96 (0.73, 1.25)
			C+D	3705		90	0.84 (0.63, 1.10)
			A+B+C+D	3712		95	0.88 (0.67, 1.16)
			Placebo	3679		107	
			C	14802		407	1.06 (0.92, 1.21)
			No *C*	14782		385	
			D	14819		369	0.87 (0.76, 1.00)
			No *D*	14765		423	
Other trials	Lamm, 1994[31]	All cause	Megadose vitamins	35	45 mos	8	0.86 (0.37, 2.01)
			RDA	30		8	
	MRC/BHF, 2002[34]		Vitamins	10269	5 yrs	1446	1.04 (0.97, 1.11)
	Nutr Rev, 1985[35]	All cause	*C*	25	1 yr	51	1.04 (0.69, 1.57)
			Placebo	23		49	
	Poulter, 1984[36]	All cause	*C*	27	5 yrs	12	1.52 (0.72, 3.23)
			Control	24		7	

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the Evidence Table.

A: retinol plus zinc; B: riboflavin plus niacin; C: vitamin C (ascorbic acid) plus molybdenum; CI: confidence interval; D: beta-carotene plus vitamin E and selenium; RR: risk ratio

Table 6. Risk Ratios for New Tumors for ATBC Trial.

Study	Lead Author, Yr	Type of Tumor	Intervention	Sample size	FU time	# of patients with new tumor	RR (95% CI)
ATBC	Albanes, 1996[24]	Lung cancer	AT	7286	6.1 yrs	204	0.98 (0.81, 1.19)
			AT+BC	7278		240	1.16 (0.96, 1.39)
			Placebo	7287		208	
	Albanes, 2000[25]	Colorectal cancer	AT	7286	6.1 yrs	29	0.78 (0.48, 1.27)
			AT+BC	7278		30	0.81 (0.50, 1.31)
			Placebo	7287		37	
	Heinonen, 1998[30]	Prostate cancer	AT	7286	6.1 yrs	43	0.64 (0.44, 0.94)
			AT+BC	7278		56	0.84 (0.59, 1.19)
			Placebo	7287		67	
	Rautalahti, 1999[37]	Pancreas cancer	AT	7286	6.1 yrs	25	0.96 (0.56, 1.66)
			AT+BC	7278		26	1.00 (0.58, 1.72)
			Placebo	7287		26	
			AT	14564		51	1.34 (0.88, 2.04)
			no AT	14569		38	
	Virtamo, 2000[38]	Urothelial cancer	AT	7286	6.1 yrs	47	1.27 (0.83, 1.95)
			AT+BC	7278		42	1.14 (0.73, 1.77)
			Placebo	7287		37	
	Virtamo, 2000[38]	Renal cell cancer	AT	7286	6.1 yrs	27	1.00 (0.59, 1.70)
			AT+BC	7278		27	1.00 (0.59, 1.71)
			Placebo	7287		27	
	Albanes 1996[24] and 2000,[25] Heinonen, 1998,[30] Rautalahti, 1999,[37] Virtamo, 2000[38]	Combined types of tumor: (lung, colorectal, prostate, pancreas, urothelial and renal cell)	AT	7286	6.1 yrs	375	0.93 (0.81, 0.81)
			AT+BC	7278		421	1.05 (0.92, 1.20)
			Placebo	7287		402	
	Alpha-Tocopherol, 1994[39]	Lung cancer	AT	14564	6.1 yrs	433	0.98 (0.86, 1.11)
			no AT	14569		443	
	Varis, 1998[45]	Carcinoma	AT	321	6.1 yrs	2	1.04 (0.15, 7.32)
			BC	329		3	1.52 (0.26, 9.03)
			AT+BC	361		4	1.84 (0.34, 10.01)
			Placebo	333		2	

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the evidence table.

AT: alpha-tocopherol; BC: beta-carotene; CI: confidence interval; FU: follow-up; RR: risk ratio

Table 7. Risk Ratios for New Tumor Outcome for Linxian and Other Trials

Study	Lead Author, Year	Type of Tumor	Intervention	Sample size	*FU time*	# of patients with new tumor	RR (95% CI)
Linxian Dysplasia	Dawsey, 1994[43]	Esophageal cancer	Supplement	392	30 mos	16	0.78 (0.41, 1.49)
			Placebo	362		19	
			Supplement	195	6 yrs	8	1.53 (0.51, 4.58)
			Placebo	186		5	
	Dawsey, 1994[43]	Gastric cancer	Supplement	43	30 mos	13	1.63 (0.75, 3.52)
			Placebo	43		8	
			Supplement	202	6 yrs	18	0.91 (0.49, 1.68)
			Placebo	194		19	
	Dawsey, 1994[43]	Overall biopsy	Supplement	400	30 mos	29	0.99 (0.60, 1.64)
			Placebo	368		27	
			Supplement	202	6 yrs	23	0.92 (0.54, 1.57)
			Placebo	194		24	
	Li, 1993[32]	All cancer	Supplement	1657	6 yrs	227	1.03 (0.87, 1.22)
			Placebo	1661		221	
	Li, 1993[32]	Esophageal cancer	Supplement	1657	6 yrs	123	0.96 (0.76, 1.22)
			Placebo	1661		128	
	Li, 1993[32]	Stomach cancer	Supplement	1657	6 yrs	96	1.19 (0.89, 1.58)
			Placebo	1661		81	
Linxian General Population	Taylor, 1994[12]	Esophageal cancer	*C*	201	6 yrs	4	1.18 (0.27, 5.20)
			No *C*	178		3	
			D	173		3	0.71 (0.17, 2.95)
			No *D*	206		5	
	Taylor, 1994[12]	Gastric cancer	*C*	205	6 yrs	6	2.71 (0.55, 13.25)
			No *C*	185		2	
			D	176		4	1.22 (0.31, 4.79)
			No *D*	214		4	
Other Trials	Lamm, 1994[31]		Megadose vitamins	35	6 yrs	14	0.50 (0.32, 0.78)
			RDA	30		24	
	MRC/BHF, 2002[34]		Vitamins	10269	5 yrs	800	0.98 (0.89, 1.08)
			Placebo	10267		817	

Additional studies for which risk ratios could not be calculated are discussed in the text and displayed in the Evidence Table.

C: vitamin C (ascorbic acid) plus additional vitamins; CI: confidence interval; D: vitamin D; FU: follow-up; RR: risk ratio

Table 8. Risk Ratios for Polyps Outcome for Vitamins C + E versus Placebo

Article	Intervention	Total n	Risk Ratio	95% CI	
Greenberg, 1994[47]	C+E only	751	1.06	(0.82,	1.37)
McKeown-Eyssen, 1988[49]	C+E only	137	0.82	(0.57,	1.18)

C: vitamin C (ascorbic acid); CI: confidence interval; E: vitamin E (alpha-tocopherol)

Table 9. Risk Ratios for Polyps Outcome for the use of vitamins C + E with carotenoids versus placebo: Pooled Results

Article	Intervention	Total n	Risk Ratio	95% CI	
Greenberg, 1994[47]	C+AT+BC	751	1.04	(0.79,	1.36)
Hofstad, 1998[48]	C+AT+BC+Ca	93	0.71	(0.50,	1.01)
Roncucci, 1993[50]	C+AT+A	209	0.16	(0.06,	0.43)
Pooled Random Effects Estimate			0.60[(1)]	(0.31,	1.16)

[(1)] Chi-squared test of heterogeneity p-value = 0.001

A: vitamin A; AT: alpha-tocopherol; BC: beta-carotene; C: vitamin C (ascorbic acid); Ca: calcium; CI: confidence interval

Figure 2. Meta-Analysis for Polyps Outcome.

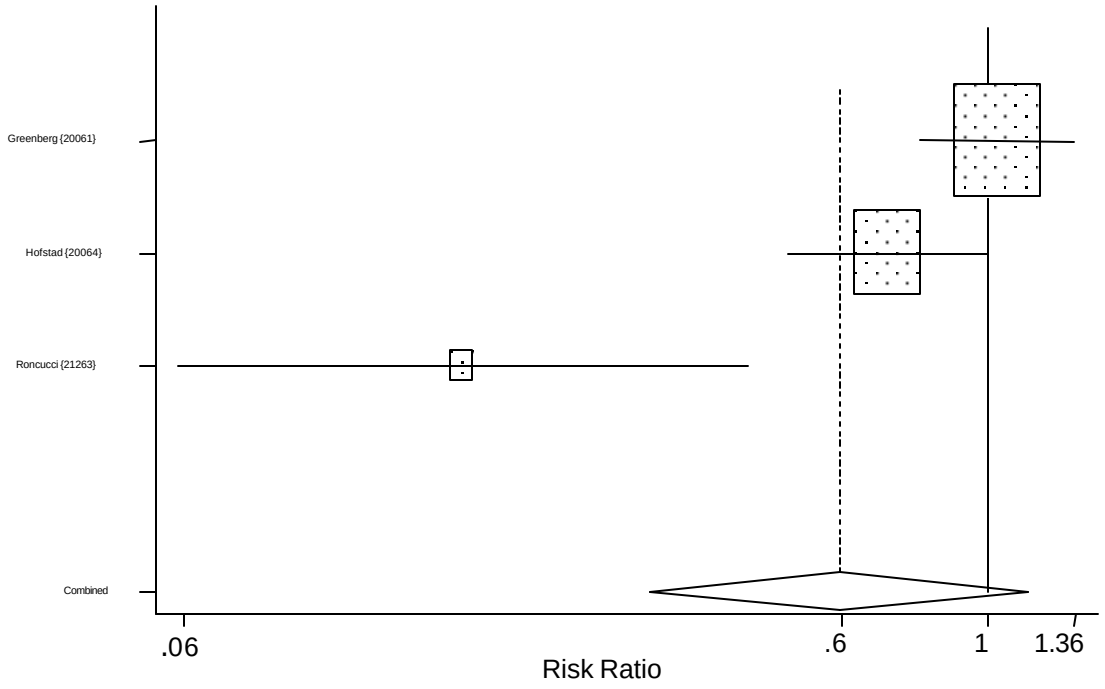
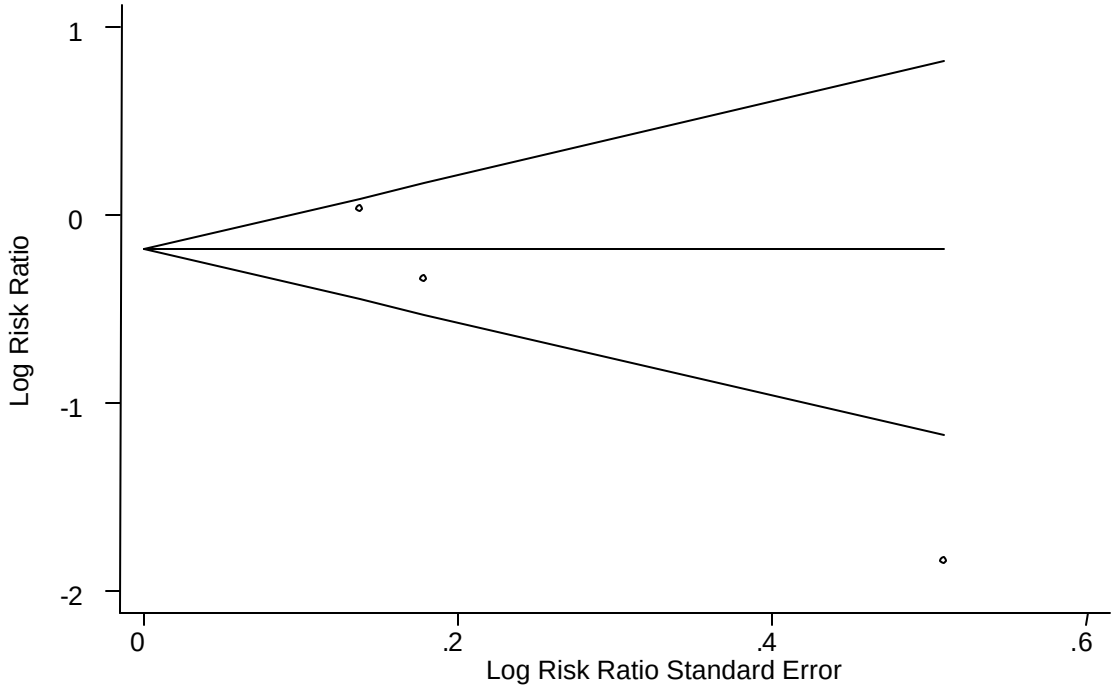
Figure 3. Publication Bias for Polyps Outcome.