# SYSTEMATIC REVIEW ON "VITAMIN E AND PREVENTION OF COLORECTAL CANCER"

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**ABSTRACT**

Colorectal cancers (CRC) are highly prevalent cancer all over the world and need appropriate and timely prevention and treatment. Since years it has been argued that antioxidant vitamins have a potential role in the prevention of several neoplasm including colorectal cancer though the answer remained controversial. Most of the observational studies in past have shown that Vitamin E has some protective effect in the primary prevention of colorectal cancer, however its exact role is not yet established. On the other hand recently conducted experimental studies have shown variable results regarding the role of vitamin E in preventing colorectal cancers. Thus this review was conducted to study the role of vitamin E in preventing colorectal neoplasm. This review study was conducted from September 2008 to February 2009. We searched multiple electronic sources including (PUBMED) MEDLINE, Cochrane Database for identifying existing Systematic Reviews, OVID data base and other library sources to identify relevant studies for this review. Data was collected using data extraction form. Meta analysis was performed in Review Manager version 4.3. We identified four trials on vitamin E role for primary prevention of CRC, includes 94069 participants (47029 in vitamin E Vs 47040 in placebo), aged 40 years or above, who were randomized to vitamin E supplement versus placebo. The outcome measure in our review was incidence of colorectal cancer in the follow up period of 7 to 10 years. We found no sufficient evidence of vitamin E role for decreasing risk of CRC incidence (RR: 0.89, CI: 0.76, 1.05; p-value = 0.18). It has been identified in the review that Vitamin E does not have protective role in the prevention of colorectal cancer. Further studies on diverse population are required to determine the role vitamin E for the primary prevention of colorectal cancer.

**Keywords**: Colorectal cancer, Vitamin E, antioxidants.

## BACKGROUND

Colorectal cancer is one of the commonly occurring cancer with increasing incidence and is considered as the major killer in western countries (Bosman *et al.,* 1995, Cancer Care Ontario, 2004). In women, it is estimated to be the second most commonly occurring cancer after breast cancer in western countries, similarly incidence is also very high in men and it is placed as third most common cancer after lung cancer and cancer of prostrate (McDonald, 2001). Estimates from USA showed that colorectal cancer is the second leading cause of death in US (Boring, 1991).

Increase in age and family history of CRC are considered as the two most important risk factors for colorectal cancer and the life time risk is as high as 5% for its development (Anne B Ballinger *et al.,* 2007). A large proportion of colorectal cancer comes originally from adenomas, yet the risk of colorectal cancer increase by many other environmental factors or medical conditions including genetic problems (Peipins, 1994). Major determinants of CRC include life style, dietary factors, co morbidities and unwanted effect of some medical interventions. One of the major problem with colorectal cancer is the lack of effective treatment, hence despite the advancement in treatment, no significant reduction in the mortality have been observed. Therefore prevention is considered as the most important measure to decrease the incidence of colorectal cancer (Lin, 2009).

Vitamins play important role in human body not only for providing nourishment to the body tissues but also protect body from several diseases including neoplasms (Donaldson *et al.,* 2004). There are several evidences about the role of different vitamins for preventing cancer growth in humans as well as other chronic diseases (World Cancer Research Fund, 1997). Many observational studies showed significant protective effect of vitamin E in the prevention of CRC and recommended its use for primary prevention of cancer (Benito *et al.,* 1993, Olsen *et al.,* 1994). One of the systematic review with large prospective cohort studies revealed that vitamin E has a protective role in cancer prevention though evidence were weak and further investigation and experimental research was suggested (Longnecker *et al.,* 1992). Later on a clinical trial was conducted on 137 patient of adenoma in 1988 (probably the first randomized trial on vitamin E efficiency for primary prevention of colorectal) looked at the effectiveness of antioxidant vitamin (Vit C and Vit E) and declared that no significant benefit of vitamin E supplements exist for preventing recurrent adenomas (Mckeown-Eyssen *et al.,* 1998). Thus contradictory statements started originating regarding the

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role of antioxidants in cancer prevention and further experimental trials were initiated. One of the latest review by Langman *et al.,* published in 1998, strongly suggested the use of vitamin E and other antioxidants for the prevention of CRC however this review was also based on evidences mostly from observational studies so the question remained unanswered. Hence it is still contradictory to conclude whether these antioxidants have some protective role in cancer prevention or not? In the recent years few large randomized controlled trials were conducted however again there is difference in their results regarding the proven efficacy of vitamins for colorectal prevention. Thus we conducted this systematic review to identify vitamin E role for primary prevention of colorectal cancer, with the help of pooled data from multiple randomized clinical trials (RCTs).

The aim of the study was to determine if vitamin E supplements help in decreasing incidence of colorectal cancer among adult population with the help of reviewing published randomized controlled trials.

## METHODOLOGY

Indexed Medline sources were searched for this review and only last ten years literature was included to limit the review to the latest mega trials conducted on vitamin E in the past ten years from Jan 1999 to Jan 2009. This is because mostly studies on vitamin E were observational before that period and in the past few years researchers shifted to experimental designs for determining role of vitamin E on CRC incidence hence we only included randomized controlled trials to present cumulative results from experimental studies.

The review was conducted by two reviewers independently which are medical scientist and public health consultants with relevant experience in clinical epidemiology. Only articles in English language, RCTs on vitamin E role for prevention of colorectal cancer, conducted and published in the last ten years were included in this review. We searched multiple electronic sources including (PUBMED) MEDLINE, Cochrane Database for identifying existing Systematic Reviews, OVID data base and other library sources to identifying relevant studies for this review. In addition Google scholar was also used though articles found were checked for their presence in other indexed sources. Keywords for MeSH terms included vitamins and cancer, antioxidants and colorectal cancer, vitamin E and colorectal cancer vitamin E and neoplasm, Vitamin E and cancer prevention.

Two authors independently reviewed the searched articles, collected data about study design, targeted population, applied intervention and the desired outcome. In the first step only titles were scanned to select articles, further selection was based on abstract and the selected article were read for methodological appropriateness. For the quality of studies, CONSORT guidelines were used to identify randomization process, blinding, treatment concealment and allocation, whether intention to treat analysis was performed or not and other criteria as in the CONSORT check list.

## DESIRED OUTCOME

Incidence of colorectal was the desired outcome from vitamin E supplement trials. Both studies with primary or secondary outcome of incidence of colorectal cancer either on male only, female only or both were included in the review. Treatment group comparisons were obtained with vitamin E supplement versus placebo or other supplement without any known interaction in factorial designs. Those RCT in which combination of other vitamins along with vitamin E was taken as exposure to determine combine vitamins effect or antioxidant effect were excluded from this review. In addition those studies with the outcome of changes at cellular level were excluded, dichotomous outcome of occur of colorectal cancer was taken as the desired outcome

## METHODS OF EVALUATING EFFECTIVENESS

A 22 items CONSORT checklist 2008 was used to assess the quality of published trials. Therefore 4 trails were selected on the given topic through screening of article (see appendix) All studies were high quality trial with CONSORT scoring ranging from 15 to 20 (Mean= 17; SD=2.2). All four trials were selected from internationally indexed journal, two from JAMA (Impact factor=24), one from Cancer causes & control (Impact factor=2.9) and one from Journal of the National Cancer Institute (Impact factor=15.9). All trials reported double blinding however only one evaluated blinding and randomization process in detail (Lippman *et al.,* 2009). Most of the studies revealed intention to treat analysis. Survival analysis was performed in each of the selected studies with reported risks in the form of hazard ratio or relative risk (Lippman *et al.,* 2009, Albanes *et al.,* 2000 and Lee *et al.,* 2005).

## RESULTS

Four trials were selected for this review in which similar outcome (incidence of colorectal cancer among vitamin E supplement group and placebo) was measured in randomized controlled trials. In total 94069 participants' data was pooled from all four studies, among them 2 were on men only (N=46566) and two studies selected women participants (47503), and the proportion of women was significantly higher than male (50.5% Vs 49.5%) with significant difference (P-value<0.001). All of the studies used double blinded, concealed treatment and were

considered as high quality trial according to CONSORT guidelines. Table.1 presented crude data of each of the studies, all had taken age group 40 years or above for their inclusion criteria. Two trials had primary outcome of incidence of CRCs (Albanes *et al.,* 2000 and Lee *et al.,* 2005), however other two trials had taken colorectal cancer as a secondary outcome however sample sizes were sufficiently enlarged to detect effective difference (Lippman *et al.,* 2009 and Lin *et al.,* 2009). Lee *et al.,* 2005 presented and analyzed rectal cancer and colon cancer incidence separately with insignificant result though in our meta analysis data was pooled together for both outcomes. Two of them (Lippman *et al.,* 2009 and Lin *et al.,* 2009) had similar vitamin E supplementation of 600 IU on alternate days (300 IU/day) one (Lippman *et al.,* 2009) used 400 IU and another used 50mg daily dosage of vitamin E in the trial (Albanes *et al.,* 2000). Although all four trials showed statistically insignificant difference regarding the incidence of CRCs however the result of two trials reported more protective effect of vitamin E as compared to placebo group (Albanes *et al.,* 2000 and Lin *et al.,* 2009). On the other hand other two trials (Lippman *et al.,* 2009 and Lee *et al.,* 2005) showed no role of vitamin in primary prevention and one trial was stopped early at 7 years instead of 12 years in the presence of insignificant findings (Lippman *et al.,* 2009). One study had large sample size in which vitamin E as well as selenium effect was determined however we used half the sample in which vitamin E only group was compared with placebo to prevent contamination of exposure (Lippman *et al.,* 2009).

**Table 1**: Characteristics of the selected studies along with their presented data and estimated results

| Study | | sex | Age group | Vit E dosage | Total participants | Intervention n/N | Controls n/N | RR (95% C.I) | Follow up |
|---|---|---|---|---|---|---|---|---|---|
| Albanes *et al* 2000 (ATBC trial) | | Male | 50 to 69 years | 50 mg/day | 29,133 | 59/14564 | 76/14569 | 0.78 (0.55-1.09) | 8 years |
| Lippman Scott *et al* (2009) (SELECT trial) | | Male | >50 years | 400 IU/day | 17433 ** | 66/8737 | 60/8696 | 1.09 (0.69-1.73) | 7 years |
| Lee *et al.*, 2005* | Colon cancer | Female | > 45 years | 600 IU every second day | 39 876 | 107/19 937 | 107/19 939 | 1.00 ( 0.77- 1.3) | 10 years |
| | Rectal cancer | | | | | 22/19937 | 33/19939 | 0.6 (0.3-1.1) | |
| Lin *et al* 2009 | | Female | >40 years | 600 IU every second day | 7627 | 17/3791 | 27/3836 | 0.63 (0.34-1.15) | 9.4 years |

*In the trial colon and rectal cancer incidence were given separately.
**Although total participants were 35533 half of them were also exposed to selenium supplement, we included only those on vitamin E supplements in comparison to placebo.

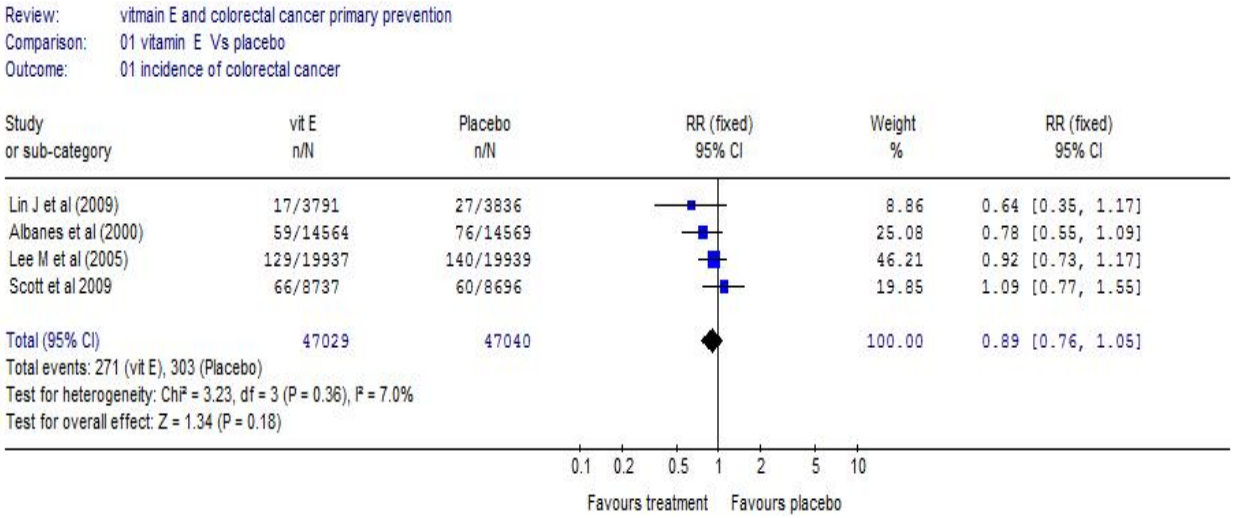


**Fig. 1**: Meta-analysis of interventional studies determining effectiveness of Vitamin E in Colorectal cancer prevention.

## ASSESSMENT OF EFFECTIVENESS

Pooled data is presented in which relative risk of individual (as all studies had prospective data) are given through Meta analysis. Studies are given along with $\chi^2$ heterogeneity test in the forest plot along with study weights using Review Manager 4.3 version. Chi square test of heterogeneity showed that the studies were comparable in terms of size, effect and outcome as shown by insignificant P-value (P-value=0.18) We used fixed effect model for these studies, though one study presented slightly different results favoring placebo yet effect shown was very small. At the bottom of forest plot diamond represented pooled confidence interval (CI) and the vertical line showing 1 relative risk (RR) representing no difference or no effect. All studies reported mild protective effect with capturing of nullified effect RR=1 within the confidence interval. Therefore combined results from the studies showed no significant protective effect of vitamin E for primary prevention of colorectal cancer (RR=0.89; CI=0.76 to 1.05).

## IMPLICATIONS FOR POLICY/PRACTICE

This review presented experimental controlled trials studies to generate concrete and latest evidences regarding the use of vitamin E for the primary prevention of colorectal cancer. The findings may have great importance for implementation and understanding of physicians, patients and general public about the use of vitamin supplements. Following are the important points identified in the review.

The major output from the review is the insignificant role of vitamin E for decreasing CRC incidence when compared with placebo in randomized controlled trials.

- The review consists of only similar kind of studies in terms of methodology, design, output and somehow vitamin E exposure was also comparable. In addition no heterogeneity was found in among the data of these studies hence more reliable results are presented.
- This review reported only incidence of colorectal cancer as a result of vitamin E supplements, yet it does not comment on vitamin E supplement role for other conditions. In addition it does not comment on any harmful effects of vitamin E supplement at continuous or high exposure (Yasunaga, 1982).
- Although the dosage in the trials were within the range of maximum daily intake of vitamin E, yet low dose supplementation along with enhanced dietary intake may have different role (Stone and Papas, 1997).

Antioxidant vitamins have been experimented in animal models yet no consistent results could be achieved regarding their role in preventing colorectal cancer at maximum administrable dose. One of the earliest experimental studies on mice showed reduced number of intestinal tumor in the interventional group of mice receiving vitamin E supplement (Cook and McNamara, 1980). Similar findings obtained from a recent laboratory study on mice showing anti tumor effect of vitamin E and its possible role in cancer prevention (Dong, 2009). The role of antioxidants at cellular level in controlling cellular growth had been observed which originates the bases of its role in cancer prevention (Gescher *et al.,* 1998), although exact mechanism and sites of action in the body has not been understood completely (Das Stone, 1994). Therefore its clinical effectiveness in primary prevention of cancer has not yet established in human experimental trials. In addition, water soluble antioxidants such as vitamin C may reveal better results in cancer prevention with little risk of high dose toxicity (Peipins *et al.,* 2003).

## FUTURE RESEARCH GUIDELINES

This review has produced evidence regarding the use of vitamin E for preventive purpose of colorectal adenoma in healthy individuals. However there is a space for further research to identify if there is a role of vitamin E in different conditions associated with colorectal cancer or in its treatment plan. In addition the evidences about protective role of vitamin E for colorectal cancer prevention came from multiple region of the world and different population, on the other hand RCTs are conducted in limited areas. Therefore it can be possible that it produce different result in different populations in the presence of environmental or genetic difference among different populations. In different ethnic groups there are again issues of implementation of findings at massive level in the presence of studies on limited population. Hence it can be recommended that more RCTs are required at different populations to produce generous results to decide whether future use of antioxidants should be stopped or continue, however our findings do not recommend its further use for preventing colorectal cancer. In addition, in the light of these results, ethical considerations are necessary for future trials as new trials for determine this outcome only may have ethical concerns. SELECT trial was stopped 5 years earlier because of insufficient justification of continue vitamin E supplementation, although their outcome of prostrate cancer, they all reported insignificant findings for colorectal cancer incidence (Lippman *et al.,* 2009). Yet we never know when new evidence appears from currently undergoing trials as primary or secondary outcome and add further to existing literature.

## CONCLUSION

The evidence presented in the review does not support the use of vitamin E for the primary prevention of colorectal cancer. Further evidence may be required to determine its effects at cellular level to determine its exact action on cancer cells production. In addition future trials may be conducted on different population to capture more generous results. Finally vitamin E supplements may produce more clear outcomes on different dosage. However grossly it does not prove to be beneficial in decreasing over all incidence of colorectal cancer among male or female in the presence of today's evidence, hence vitamin E supplements may not be irrationally recommended to general population.

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## LIST OF ABBREVIATIONS

CRC = Colorectal cancer
CONSORT = Consolidated Standards of Reporting Trials
JAMA = Journal of American Medical Association
MeSH = Medical subject headings
RCT = Randomized clinical trial
RR = Relative Risk
SELECT trial = Selenium and Vitamin E Cancer Prevention Trial
$\chi^2$ = Chi-square test

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