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Ginkgo biloba and risk of cancer: Secondary Analysis of the Ginkgo Evaluation of Memory (GEM) Study

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Abstract

Purpose—Evidence from *in vitro* and *in vivo* studies suggests that *Ginkgo biloba* has cancer chemopreventive properties, but epidemiological evidence is sparse. We analyzed cancer as a secondary endpoint in the Ginkgo Evaluation of Memory (GEM) Study, the largest randomized, double-blind, placebo-controlled clinical trial of *Ginkgo* supplementation to date.

Methods—A total of 3,069 GEM participants 75+ years of age were randomized to twice-daily doses of either 120mg *Ginkgo* extract (*EGb 761)* or placebo and followed for a median 6.1 years. We identified hospitalizations for invasive cancer by reviewing hospital admission and discharge records for all reported hospitalizations over follow-up. Using an intention-to-treat approach, we compared the risk of cancer hospitalization between participants assigned to treatment and those assigned to placebo.

Results—During the intervention, there were 148 cancer hospitalizations in the placebo group and 162 in the *EGb 761* group (Hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.87–1.36; p=0.46). Among the site-specific cancers analyzed, we observed an increased risk of breast (HR, 2.15; 95% CI, 0.97–4.80; p=0.06) and colorectal (HR, 1.62; 95% CI, 0.92–2.87; p=0.10) cancer, and a reduced risk of prostate cancer (HR, 0.71; 95% CI, 0.43–1.17; p=0.18).

Conclusions—Overall, these results do not support the hypothesis that regular use of *Ginkgo biloba* reduces the risk of cancer.

Keywords

Ginkgo biloba; randomized controlled trial; breast cancer; prostate cancer; complimentary and alternative medicine

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INTRODUCTION

Ginkgo bIloba extract is among the most commonly prescribed medications in Germany and France 1 and one of the most widely used herbal dietary supplements in the United States.2 The standardized commercial *G. biloba* extract, EGb 761, contains various biologically active constituents, with purported therapeutic benefits in the treatment or prevention of claudication, cognitive decline, dementia, and cerebral insufficiency.3 Data from studies of *in vitro* and experimental model systems suggest that *G. biloba* may also have effects on angiogenesis, DNA damage, cell proliferation and death, and reactive oxygen species consistent with cancer preventive properties,4 but data from human studies is sparse. Epidemiological evidence is limited to a single population-based case-control study of 1,389 women that reported an inverse association between regular use of *G. biloba* and risk of ovarian cancer (OR=0.41; 95%CI: 0.20–0.84).5 In this paper we report cancer as a secondary endpoint from the Ginkgo Evaluation of Memory (GEM) Study, the largest double-blind, randomized controlled trial of *Ginkgo* supplementation to date.

METHODS

The GEM Study was a randomized, double-blind, placebo-controlled clinical trial of *G. biloba* for the prevention of dementia conducted at 4 clinical centers across the US between 2000 and 2008. Recruitment, randomization, and follow-up procedures have been described previously.6,7 Briefly, after obtaining signed informed consent, 3069 participants, aged 75 years or older at study entry, were randomized to twice-daily doses of either 120mg *EGb 761*, or placebo. Following the baseline examination, participants completed clinic visits at 6-month intervals, with telephone contacts at the intervening 3 month intervals. The study protocol was approved by the institutional review boards of all universities involved in the study in addition to the National institutes of Health. Analyses of the primary endpoint of incident dementia found that *G. biloba* was not effective in reducing the risk of dementia in persons 75 years and older.7

A comprehensive medical history questionnaire was administered to participants at baseline during which individuals were asked to report any cancer diagnoses occurring in the 5 years prior to enrollment. Information about morbid events, including any hospitalizations, was collected quarterly during the clinic visits and intervening phone calls. Admission and discharge abstracts were obtained for all reported hospitalizations and we used these records to identify hospitalizations for invasive cancer. Each cancer was identified by its primary site, and each primary was counted only once. Non-melanoma skin cancers and benign neoplasms were disregarded.

Statistical Analysis

We conducted analyses using an intention-to-treat approach. *A priori*, we defined two periods of observation for use in analyses, one beginning at randomization, and a second beginning one year post-randomization, based on the reasoning that treatment assignment would be less likely to be related to any cancers occurring in the short term. For the primary analysis, time at risk was calculated as the time elapsed between randomization and the earliest of: 1) admission date for cancer hospitalization, 2) date of death, 3) date of last contact, or 4) end of follow-up. In a secondary analysis, time at risk was calculated as above, but began one year post-randomization. Participants were censored at the date of last contact, end of follow-up, or death. We used Cox proportional hazards to compute hazard ratios and 95% confidence intervals comparing the risk of cancer associated with assignment to *EGb 761* or to placebo. In addition to analyzing the overall occurrence of cancer, we also analyzed site-specific cancers for sites with at least 20 occurrences. All models were adjusted for clinical center, which was a stratification variable used in the randomization.

All participants were included in the main analysis regardless of past history of cancer, but as a sensitivity analysis we repeated the analysis after excluding participants reporting a history of cancer in the 5 years prior to enrollment. $P<0.05$ was considered statistically significant, and all tests were 2-sided.

RESULTS

Demographic, lifestyle, and medical characteristics of participants at baseline were similar among those randomized to *Ginkgo* and to placebo. Median follow-up was 6.1 years. At the end of the trial, there was no significant difference between treatment groups in the proportion of active participants who were taking their assigned study medication (63.9% of those assigned to placebo and 59.3% of those assigned to *Gingko* were compliant with the assigned intervention).

During the intervention, there were 310 cancer hospitalizations, 148 in the placebo group and 162 in the *EGb 761* group (Table 1). The rate of cancer overall was similar among the two treatment groups (Hazard ratio [HR], 1.09; 95% CI, 0.87–1.36; p=0.46). Breast (HR, 2.15; 95% CI, 0.97–4.80; p=0.06) and colorectal cancers (HR, 1.62; 95% CI, 0.92–2.87; p=0.10) were elevated among participants in the *EGb 761* group, while prostate cancer was reduced (HR, 0.71; 95% CI, 0.43–1.17; p=0.18). Results were similar for the observation period beginning one year post-randomization in the analysis, although the hazard ratio estimates were moderately attenuated for colorectal cancer (HR, 1.27; 95% CI, 0.68–2.40) and strengthened for breast cancer (HR, 2.50; 95% CI, 1.03–6.07). Results were also similar when we excluded the 564 participants (18%) reporting a history of cancer in the 5 years prior to enrollment, though in this subset of data breast cancer estimates were attenuated and colorectal cancer estimates were strengthened. Hazard ratio estimates (95% CI) among participants cancer free for 5 years prior to enrollment were: all sites, HR=1.05 (0.81–1.36); prostate, HR=0.62 (0.30–1.28); lung, HR=0.86 (0.47–1.60); colorectal, HR=2.15 (1.11–4.15); urinary, HR=0.85 (0.41–1.80); breast, HR=1.55 (0.66–3.63); lymphoma and leukemia, HR=0.99 (0.41–2.37).

DISCUSSION

In this analysis of data from the largest randomized clinical trial of *G biloba* to date, we found little evidence of a protective role of *EGb 761* in cancer occurrence. In contrast, there was a statistically significant 2-fold increase in breast cancer among women assigned to *EGb 761* when we excluded cancer cases ascertained during the first year following randomization, and a 2-fold increase in colorectal cancer in participants cancer-free for 5 years prior to enrollment. Despite the statistical significance of these estimates, these findings should be considered in the context of the small sample size and low prior probability of a true positive association, which increases the likelihood of a false positive finding.8 The reduction in prostate cancer is intriguing, in light of evidence that *Ginkgo* may possess antithrombotic properties9 10–12 and reports suggesting a decreased risk of prostate cancer associated with the use of warfarin,13,14 another antithrombotic agent. However, we cannot rule out chance as an explanation for this finding. Should the breast, colorectal or prostate cancer associations be replicated in another study, it would be of great clinical and public health significance given the high prevalence of these cancers.

The major strength of this study was that participants were randomized to treatment groups, minimizing the potential for confounding by measured or unmeasured cancer risk factors. As with any clinical trial, participants were carefully monitored for adverse events on a regular basis and it is unlikely that any hospitalizations were missed. Cancer is a well-defined endpoint easily identified in hospitalization records minimizing the likelihood of

misclassification of the outcome. There was a high rate of treatment adherence among trial participants and the 240-mg dose of *EGb 76* is a dose commonly used, enhancing the generalizability of the findings. The incidence of cancer in the US is highest among adults aged 75+ (incidence=2,279 per 100,000)15, therefore the study population, whose mean age was 78.6 at randomization, is a relevant population for this analysis.

Several study limitations should also be considered when interpreting the results. We had low statistical power to detect differences in site-specific cancers between treatment groups. Because we relied on hospitalization records to identify participants with cancer, we were unable to uniformly identify cancers at the time of diagnosis for all participants, and were unable to identify cancer cases not requiring hospitalization. Hospitalized cancers represent only a subset of all malignancies diagnosed over follow-up, particularly among sites where non-surgical treatment options are common. Under-ascertainment of cancer cases and potential lags between date of diagnosis and date of hospitalization would result in the misclassification of some cancer patients as cancer-free in the regression risk sets. However, due to the random allocation of participants to treatment groups, we would expect this misclassification to be non-differential with respect to treatment assignment and result in a bias towards the null. Finally, the extract and dose used were not optimized for cancer prevention, and our follow-up period may have been too short to observe any beneficial effects of *EGb 761* on cancer occurrence.

Key points

- Results of this secondary analysis of randomized controlled trial data do not support the hypothesis that consumption of *Ginkgo biloba* reduces the risk of cancer.

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Appendix

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Table 1

Frequency of cancer hospitalization by study drug assignment, and hazard ratios comparing *Ginkgo biloba* to placebo.

Cancer site	Number with cancer hospitalization		HR (95% CI)[1]	p-value
	Placebo	Gingko biloba		
Observation period beginning at randomization				
Any	148	162	1.09 (0.87–1.36)	0.46
Prostate	36	27	0.71 (0.43–1.17)	0.18
Lung	29	26	0.90 (0.53–1.52)	0.68
Colorectal	19	31	1.62 (0.92–2.87)	0.10
Urinary	18	22	1.21 (0.65–2.26)	0.54
Breast	9	18	2.15 (0.97–4.80)	0.06
Lymphoma & Leukemia	12	13	1.07 (0.49–2.34)	0.87
Pancreatic	6	10		
Oral	5	2		
Ovarian	2	5		
Other	17	18		
Observation period beginning one year after randomization				
Any	138	150	1.07 (0.85–1.35)	0.55
Prostate	35	25	0.68 (0.41–1.14)	0.14
Lung	27	27	1.00 (0.58–1.70)	0.99
Colorectal	17	22	1.27 (0.68–2.40)	0.46
Urinary	18	18	0.99 (0.52–1.91)	0.98
Breast	7	16	2.50 (1.03–6.07)	0.04
Lymphoma & Leukemia	11	13	1.17 (0.52–2.61)	0.71
Pancreatic	5	10		
Oral	4	1		
Ovarian	2	5		
Other	21	19		

[1] adjusted for clinical center