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The Effect of Phytochemicals Intake from Green Leafy Vegetables on the Incidence of Gastrointestinal Cancers: A Meta-Analysis

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Abstract- Study objective was to hypothesize that the consumption of green leafy vegetables (GLV), including cruciferous vegetables (CV), significantly reduces the incidence of gastrointestinal cancers. The hypothesis was answered by using the experimental approach of meta-analysis by synthesizing relevant worldwide studies that address the association between the consumption of GLV and risk of incidence of the disease. The random effect model was used and indicated an overall odds ratio effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on gastrointestinal cancer as: OR = 0.651 (95% CI. 558 to .760), p<.001. These results indicate the highest quartile or quintile of intake of GLV and/or CV compared to lowest in take is associated with a significant 34.9% lower odds of incidence from gastrointestinal cancers.

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I. Introduction

Gastroenterology is the branch of medicine focused on the digestive system and its disorders. Diseases affecting the gastrointestinal (GI) tract, which include the organs from mouth to anus, normally include pharynx, esophagus, stomach, pancreas, liver, gallbladder, small and large intestines. Physicians practicing in the field of gastroenterology are called gastroenterologists and have additional specialized training (fellowship) in Gastroenterology. Cancer can invade or spread to all organs of the GI tract. Reducing incidence of these cancers should be a worldwide concern.

Colorectal cancer is also known as colon cancer, rectal cancer, or bowel cancer and develops in the colon sections or rectum which are divisions of the large intestine. This type of cancer is caused by abnormal growth of cells that can invade and spread to other parts of the body (Colon Cancer Treatment (PDQ®), 2014)[1]. This same website lists symptoms that may include weight loss, blood in stool, change in bowl movements, and weights loss causing fatigue. Most colorectal cancers are caused by lifestyle factors and increasing age, with only a small number of incidences due to genetics and the most common risk factors are diet, lack of exercise, obesity, smoking, and alcoholism (Colon Cancer Treatment (PDQ®), 2014)[1]. Worldwide, colorectal cancer is reported as the third-most common cancer in men, the second-most common cancer in women, and the fourth-most common cause of cancer mortality (Xie & Chang, 2016)[2]. In 2015, these same authors reported that there were about 1.5 million patients worldwide, which accounted for about 10% of total cancer cases, and estimated colorectal cancer caused deaths were an estimated 753,000. It is imperative that medical doctors and surgeons should emphasize on this failure of existing chemotherapeutics against GI cancers and start using complementary/alternative therapeutics to prevent and treat these deadly cancers.

Pancreatic cancer progresses quickly and has an extremely high mortality rate in the U.S. and is the fourth highest cancer fatality rate of all cancers (Chan, Wang, & Holly, 2005)[3]. In 2005, it was estimated that about 32,180 pancreatic cancer patients will be diagnosed, with most of them dying from this cancer with the 5-year survival rate being only 4% (Chan et al., 2005)[3]. These high mortality rates are due to late-stage diagnosis, including lack of effective treatment. Not much is known about the epidemiology of this deadly disease, and like many cancers, it is age-dependent with over 90% of the patients diagnosed at age 50 and older (Chan et al., 2005)[3]. Pancreatic cancer is one of the most rapidly fatal cancers, yet little is known about the primary cause and prevention of this devastating disease.

Pharyngeal cancers originate in the epithelial cells lining the nasopharynx, oropharynx, and/or the laryngopharynx. These cancers are relatively rare, with 130,000 new cases diagnosed worldwide each year (Heck et al., 2008)[4]. The Indian subcontinent has among the highest rates of hypo pharyngeal cancer worldwide; due in part to the common use of chewing tobacco products, and the purpose of their study was to examine the associations between the Indian diet and hypo pharyngeal cancer(Heck et al., 2008)[4].

Based on estimates, a total of 989,600 new cancers of the stomach (gastric cancer) cases and 738,000 deaths occurred in 2008, which accounted for 10% of the total cancer deaths worldwide (Zhao et al., 2014)[5]. Despite advances in treatment, survival rate of

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patients with gastric cancer remains low and it is vital to detect early stages of this cancer by developing new diagnostic and therapeutic strategies for this disease (Zhao et al., 2014)[5]. Esophageal cancer is the sixth most common cancer worldwide, and large geographical variations in its occurrence indicates that environmental exposures are casually important (Phukan, Chetia, Ali, & Mahanta, 2001)[6]. Squamous cell carcinoma of the esophagus occurs at a high frequency in many developing countries such as Iran and northcentral China (Yamaji et al., 2008)[7]. Prevalence of tobacco smoking and alcohol drinking in these regions are not markedly high, so attention has focused on roles of diet, particularly the tendency toward low intake of fruits and vegetables, and the relationship of esophageal cancer incidence.

In recent years, the role of dietary habits in the development of GI tract cancers has received much attention in the scientific community (Zanini, Marzotto, Giovinazzo, et al. 2015)[8]. Dietary habits as risk factors of cancer have been studied by several researchers in relation to the consumption of foodstuffs. This study will contribute to people's understanding of the importance of a daily intake of green leafy vegetables (GLV), including cruciferous vegetables (CV). Studies indicate long-term intake of GLV, CV, and the micronutrients they contain may reduce risk of Type 2 diabetes, cardiovascular disease and some types of cancers (Carter, Gray, Troughton, et al. [9], 2010; Joshipura et al.,[10]2009; Smith-Warner et al., 2001)[11]. Limited knowledge about the importance of GLV consumption appears to be a serious worldwide health problem. This meta-analysis study further emphasized the importance of this association by synthesizing multiple source studies researched worldwide on the topic of GLV intake and incidence of GI tractcancers.

GLV are leaf vegetables, greens, vegetable greens, leafy greens or salad greens. They come from a very wide variety of plants all over the world, with nearly one thousand species of plants with edible leaves are known. GLV contain elements and phytochemicals that may reduce the incidence of cancer, and these same GLV are high in Vitamin C, Vitamin E, Vitamin K, and Vitamin A (USDA National Nutrient Database for Standard Reference, Release 24, 2002)[12].

CV are from the family *Cruciferae* which are widely cultivated, with many genera, species, and cultivars being raised for food production such as cauliflower, cabbage, cress, bok choy, broccoli, kale, collard greens and similar leafy vegetables and their roots such as turnips and radishes. Most researchers evaluating the association of fruit and vegetable intake with the risk of cancer place GLV and CV into two separate food categories even though most CV have edible green leaves. They are separated because only CV contain isothiocyanates which are plant phytochemicals that are known to possess the ability to prevent and inhibit tumorigenesis (Øverby, Thangstad, & Bones, 2015)[13].

Will the consumption of GLV including CV will significantly reduce the incidence of GI tract cancers is the research question of this study? There is a need to research peer-reviewed journals to investigate case-control studies dealing with GLV intake and the incidence of these deadly diseases. This meta-analysis was used to investigate the effects of daily GLV, including CV, intake on the incidence of these type cancers, not just in the United States but worldwide, and to show if this relationship is a significant one. This meta-analysis research approach filled a knowledge gap by combining data from multiple studies to a common effect size and statistically examining relations between study characteristics and findings. Findings between these different studies were compared by transforming the results into a single common effect size to better understand the apparent contradictions in prior research findings.

II. Methods and Materials

Searching for relevant studies was primarily performed by computer search engines. PubMed Central, Academic Search Complete, Medline, ProQuest Central, Science Direct, Google, and Yahoo online were the most frequently used online periodical databases. The criteria for including studies in the meta-analysis included: (1) those occurring between 1980 to 2016; (2) those appearing full-text in scholarly journals; (3) the collection of primary studies had to be a collaborative case-control design; (4) those including relations between similar independent variables (GLV intake levels including CV) and dependent variables (incidence of GI tract cancers); (5) all studies had to measure GLV consumption, which was estimated by highest versus lowest quantiles (quintiles, or quartiles, or tertiles); (6) those that reported an effect size of: odds ratio (OR)and their respective 95% confidence intervals (CI) data; and (7) source studies collected in this meta-analysis had to use logistic regression or Cox regression models to control for confounding or interaction variables and the results were expressed as adjusted effect size ratios if needed.

All meta-analysis calculations were performed by the software package Comprehensive Meta-Analysis Version 2 by Biostat (CMA v.2). CMA v.2 was developed specifically for use in meta-analysis. These calculations include determining effect sizes OR and their 95% CI), heterogeneity of the studies, relative weights for each study, significance (*p*) for each study, and for determining methods for detecting the presence of publication bias and assessing its impact on the meta-analysis. CMA v.2 was also used to create a high-resolution plot (Forest plot) that shows all the combined studies, their p-value, common effect size, 95% CI for

each study, relative weights for each study, and either a fixed effect model or random effect model. Borenstein, Hedges, Higgins, et al. (2009)[14]write that the selection of a model must be based on the question of which model fits the distribution of effect sizes, and when studies are collected from published literature, the random-effects model is a more plausible match for the meta-analysis. Since all studies were collected from full-text in scholarly journals, the random-effects modelwas chosen for this study.

The relative weights for each study were calculated by the CMA v.2 software package. Small studies tend to have wide confidence intervals and large studies tend to have narrow confidence intervals with larger studies given greater percent relative weights (Higgins, Hedges, Borenstein, et al., 2009)[15]. An effect size of 1.00 represents no treatment effect. Whereas when the effect size falls below 1.00, this indicates participants who consumed GLV in the highest quartile were less likely to develop cancer. If the effect size falls above 1.00, this indicates study subjects were more likely to develop the disease due to GLV intake in the highest intake quartile. The 95% CI bounding in each study reflects the precision of the estimate, with small studies tending to have wide 95% CI and large studies tending to have narrow 95% CI (Higgins et al., 2009)[15]. The use of 95% CI in this meta-analysis was used, so each meta-analysis performed in this study was statistically significant ($p < .05$) if and only if the confidence interval excluded the null value of 1.0 for each effect model synthesized (Higgins et al., 2009)[15]. The conventional value of significance level for this meta-analysis was pre-set to an alpha of 0.05 (Stigler, 2008)[16].

CMA v.2 allows the meta-analyst to record data by subgroups within the study. Some studies collected in this meta-analysis used subgroups, e.g., male, female, GLV, CV, never smoked or chewed tobacco, and ever smoked or chewed tobacco. In this study, it emerged that the effect sizes were not comparable for each subgroup and that the treatment effect varied as a function of each subgroup, so it was decided to use the subgroup as the unit of analysis. This required calculating separate effect size (utilizing the CMA v.2 software) for subgroups within each study, which recorded as many as four treatment effects for each study. CMA v.2 was also used to detect the possible presence of publication bias. All studies used in this meta-analysis were examined using a funnel plot of the natural logarithm of the effect size versus its precision (1/standard error). The plot by precision is the traditional form (Borenstein, Hedges, Higgins, et al., 2009)[14]. Note in Figure 1 that the large studies appear toward the topof the funnel plot graph, and tend to cluster near the mean of the log odds ratios in the relationship between the studies. The smaller studies appear toward the bottom of the funnel plot, and since there is more random variation in smaller studies, they are dispersed across a wide range of log odds ratios. In the presence of publication bias, the bottom of the funnel plot would tend to show a higher concentration of studies on one side of the mean than the other (Borenstein et al.2009)[14].These same authors write that this would reflect the fact that smaller studies are more likely to be published if they have smaller than average OR, which makes them more likely to meet the criterion for statistical significance. In the absence of publication bias the studies will be distributed symmetrically about the mean of the log odds ratios.

III. Data Analysis and Results

Over a four-year search period (2012-2016), thousands of scientific papers were reviewed for this meta-analysis. Table 1 shows the total number of collected studies (N=14) that were relevant and reviewed in this meta-analysis. Fourteen case control studies were combined in meta-analysis that examined the relationship between GLV and CV intake and the incidence of GI tract cancers and used OR as the effect size.

Research Question: Does an increased intake of GLV and/or CV significantly reduce incidence of GI tract cancers? Fourteen studies met the inclusion criteria that investigated the relationship between the incidences of GI tract cancers with the consumption of GLV and/or CV. The seven cancers were rectal, colon, colorectal, pancreatic, pharyngeal, stomach, and esophageal. Figure 2 is a Forest plot showing relative weight percentages of the 14 studies with similar odds ratios and a random effect model was used to combine results from the studies. Table 1 lists the 14 studies, locations of the participants, subgroups, number (N) of participants for each study (N = cases + controls), and cancer types. The random effect model was selected for combining the source studies. Subgroups GLV, CV, men only, women only, colon cancer, rectal cancer, ever tobacco, never tobacco, colorectal cancer, and stomach cancer, were not combined in six of the studies to calculate as many as four treatment effects for each study as shown in Figure 2 and Table 1. The random effect model results, $OR = 0.651$ (95% *CI* .558 to .760), $p < .001$, indicates the highest quartile or quintile of intake of GLV and/or CV compared to lowest in take is associated with a significant 34.9% lower odds of incidence from these seven different cancers. Figure 1 shows possible absence of publication bias in the 14 cancer studies with the studies distributed symmetrically about the mean of the log odds ratios.

IV. Discussion

A noteworthy finding of this meta-analysis study is the protective effect associated with high consumption of GLV including CV. These vegetables are

a characteristic and traditional dietary habit of worldwide populations. It has been previously postulated that this could help explain the low cancer incidence rates observed in populations that consume these vegetables. The role of diet in the causation of human disease is complex, partly because diet and dietary habits include a wide variety of foods and because the methods by which these habits can be measured are cumbersome as well as difficult to apply to many individuals. This study has provided some clues for further investigation into the role of GLV intake and how it affects gastroenterologicalcancer occurrence. Meta-Analysis is a collection of systematic techniques for resolving apparent contradictions in research findings. This meta-analysis translated results from 14 different studies to a common metric and statistically explore relations between study characteristics and findings. Ameta-analysis on a given research topic is directed toward the quantitative integration of findings from various studies, where each study serves as the unit of analysis. The findings between studies are compared by transforming the results to a common single metric called an effect size (Shachar, 2008, pp. 3-4)[17]. Advantages of this meta-analysis is to increase validity of research by applying objective formulas to synthesize data across studies rather than using data from a single study and control for between-study variation (Borenstein, Hedges, Higgins, et al. 2009)[14].

The fourteen case-control studies included 24,205 case participants and controls, with 8,182 case participants having seven different type cancers. The research question of this study was; does an increased intake of GLV including CV significantly reduce the incidence of these seven cancers? The random effect model indicated an overall OR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on cancer as: $OR = 0.651$ (95% CI .558 to .760), $p < .001$, showing 34.9% lower odds that an intake of GLV significantly reduces the incidence of these cancers in the highest intake category as compared to the lowest.

a) Aggregation of Studies Encompassing Various Cancer Diseases

This meta-analysis study could be limited by the aggregation of studies encompassing various cancer diseases. It is important to know which specific cancers are affected by a dietary factor to gain further knowledge into potential disease causes. However, the prevention of overall cancer diseases by diet may be of higher interest for any healthy population than the targeted recommendations for prevention of a specific cancer (Von Ruesten, Feller, Bergmann, et al, 2013)[18]. Hung et al. (2004)[19] evaluated the relationship between fruit and vegetable intake and the incidence of CVD, total cancer, and other deaths from other causes in two prospective cohort studies. Von Ruesten et al. (2013)[18]also combined overall chronic diseases, type 2 diabetes, overall CVD, and overall cancers in their published article on the relationship of diet and disease incidence which concluded that from a public health perspective, it would be better to pursue the primary prevention of several types of aggregated disease outcomes. This meta-analysis presented both overall and disease-specific results.

b) Incidence of Cancers and GLV Intake

Cancer is a group of over 100 different types of malignancies and there are several potential substances in GLV and CV that may exhibit anticancer effects (Rajalakshmi & Agalyaa, 2010)[20]. GLV are typically high in dietary fiber, iron, calcium, and very high in phytochemicals and nutrients such as vitamin C, carotenoids, lutein, folate, magnesium as well as vitamin K. The primary dietary source of vitamin K is generally GLV and both in vitro in vivo studies have shown that vitamin K exhibits anticancer effects (Chlebowski, Akaman, & Block, 1985) [21]. Vitamin K has also been shown to inhibit the growth of mammalian tumor cells in culture (Prasad, Edwards-Prasad, & Sakamoto, 1981)[22]. Also, GLV are high in carotenoids such as beta-carotene and in animal experiments they were shown to suppress liver carcinogenesis (Moreno et al., 2002)[23]. Carotenoids have antioxidant potential in the scavenging of harmful free radicals (Krinsky, 1989)[24] and they appear to play an important role in the prevention of hepatitis virus-related liver carcinogensis (Kurahashi et al., 2009)[25]. Rajalakshmi and Agalyaa (2010)[20] found that watercress (*Nasturtium officinale)* has an anti-cancer effect in their study of oral cancer. Watercress is one of the richest sources of dietary phenethyl isothiocyanates and they found it inhibited a chemical in tobacco that may cause oral cancer. Also, in several epidemiological studies, high intake of calcium has been associated with reduced risk of colorectal and breast cancer (Martinez et al., 1996[26]; Shin et al., 2002)[27]. It has been hypothesized that calcium could be the mechanism behind these protective effects by reducing fat induced cell proliferation by maintaining intercellular calcium concentrations (Lipkin & Newmark, 1999)[28].

c) Phytochemicals

Further study in the twenty first century should be focused on conducting extensive research to discover phytochemicals connections to disease prevention because solid evidence is lacking (DeBruyne, Pinna, & Whitney, 2011)[29]. Researchers are just beginning to understand and theorize how a small percent of the different phytochemicals in GLV work. There are potentially thousands of phytochemical compounds from extracts of plant roots, leaves, and stems that have shown promising potential as anticancer drugs, or for serving as lead compounds in the synthesis of new drugs (Smith, 1998[30]; Buring &

Hennekens, 1995[31]; Park et al., 2013)[32]. The potential is here just waiting for new researchers to cure cancer, type 2 diabetes, and CVD via new phytochemical drug discoveries. Table 2 shows a small sampling of phytochemical compounds and their possible effects on reducing incidence of cancers.

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Author Contributions

Dr. Richard Lee Pollock was sole author of this manuscript and was sole writer and researcher.

Conflicts of Interests

No conflict of interests is declared with this research.

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Ethical Approval

IRB at Trident University International ethically approved the content of this meta-analysis (no human subjects used).

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Table 1: Number (N) of participants per study (N = cases + controls),location of studies, cancer type, and subgroups for each study

Study	N	Location	Type of Cancer & Subgroups
Glynn et al. (1996)1	420	Finland	Colon, GLV
Glynn et al. (1996)2	420	Finland	Rectal, GLV
Wu et al. (2009)1	2281	USA	Colorectal, GLV
Wu et al. (2009)2	2281	USA	Colorectal, CV
Slattery et al. (2000)	3838	USA	Colon, CV
Annema et al. (2011)	1773	Australia	Colorectal, GLV
Vogtmann et al. (2014)	1013	China	Colorectal, CV
Hu et al. (2007)1	4477	Canada	Rectal, Women, CV
Hu et al. (2007)2	4477	Canada	Rectal, Women, GLV
Hu et al. (2007)3	4477	Canada	Rectal, Men, CV
Hu et al. (2007)4	4477	Canada	Rectal, Men, GLV
Chan et al. (2005)1	2233	USA	Pancreatic, GLV
Chan et al. (2005)2	2233	USA	Pancreatic, CV
Olsen et al. (1989)	432	USA	Pancreatic, CV
Jansen et al. (2011)	1367	USA	Pancreatic, GLV
Heck et al. (2008)1	1231	India	Pharyngeal, GLV, Never Smoked
Heck et al. (2008)2	1231	India	Pharyngeal, CV, Never Smoked
Heck et al. (2008)3	1231	India	Pharyngeal, GLV, Ever Smoked
Heck et al. (2008)4	1231	India	Pharyngeal, CV, Ever Smoked
Liu et al. (2012)	1200	China	Nasopharyngeal, GLV
Hara et al. (2003)1	436	Japan	Gastric, CV
Hara et al. (2003)2	436	Japan	Colorectal, CV
Phukan al. (2001)	1506	India	Esophageal, GLV
Cheng et al. (1992)	1998	China	Esophageal, GLV

Table 2: Sampling of phytochemicals and possible cancer reducing effects (from DeBruyne, Pinna & Whitney, 2011)

Name	Possible Effects
Carotenoids	Act as antioxidants; possibly reduce risk of cancer
Flavonoids	Act as antioxidants; may scavenge carcinogens
Indoles	May trigger production of enzymes that block DNA damage from carcinogens
Isothiocynates	May inhibit enzymes that activate carcinogens and detoxify carcinogens
Organosulfur	May speed production of carcinogen-destroying enzymes
Phenolic acids	May trigger enzyme production to make carcinogens water soluble to excrete
Phytoestrogens	May reduce cancer cell survival
Phytoestrogens	Block estrogen activity in cells, possibly reducing risk of colon cancer
Protease inhibitors	May suppress enzyme production in cancer cells, slowing tumor growth
Saponins	May interfere with DNA replication, preventing cancer cell from multiplying
Tannins	May inhibit carcinogen activation and cancer promotion; act as antioxidants

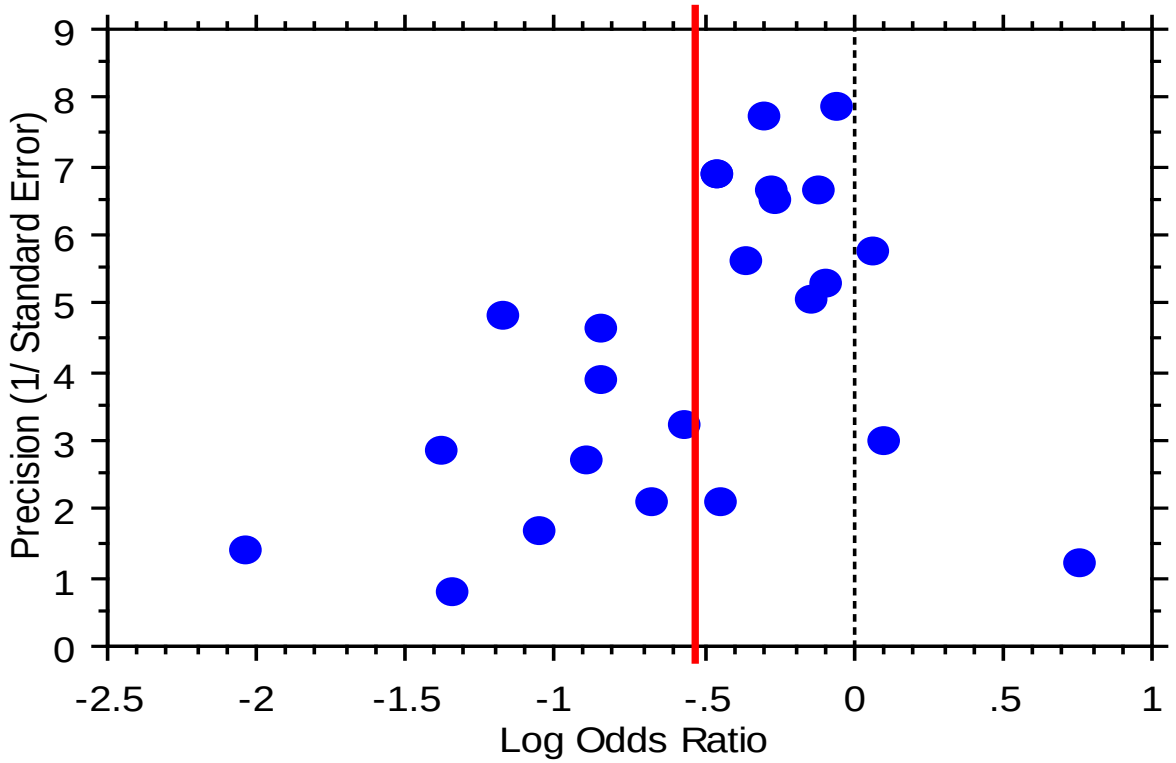

Figure 1: Funnel plot showing 14 case-control studies with 10 study results on the left of mean log odds ratio (-0.536) and 14 study results on the right signifying possible absence of publication bias

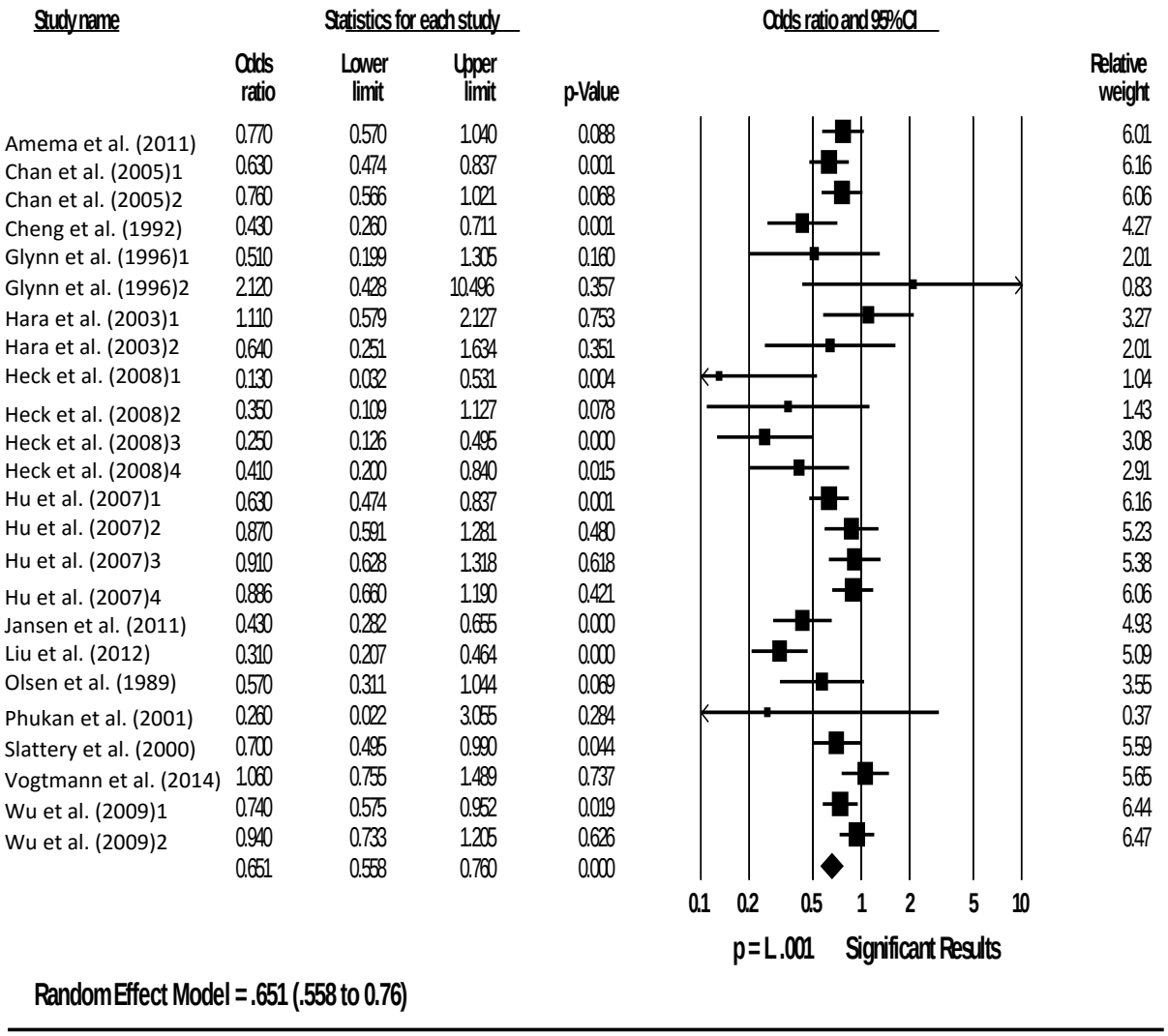

Figure 2: Forest plot showing a significant 34.9% lower odds of incidence of cancer by consuming a high quantile intake of GLV and/or CV as compared to the lowest intake