The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta-Analysis

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Abstract

Study objective was to hypothesized that the consumption of green leafy vegetables (GLV), including cruciferous vegetables (CV), significantly reduces the incidence of urothelial 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. Three models were used, and the first indicated an overall odds ratio effect size of the ?almost every day? highest vs. lowest quantile intake category of GLV on urothelial cancer as: OR = 0.749 (95

Index terms— green leafy vegetables; cruciferous vegetables; random effect model; effect size; forest plot; meta-analysis.

1 I. Introduction

istologically, urothelial cancer strikes the urinary bladder, ureter, and renal pelvis (kidney). Urothelial cancer generally originates in the mucosa of the lower urinary tract. Urothelial cancer is the 7 th most common worldwide cancer among men, accounting for about 200,000 new annual cases (Zeegers, Goldbohm, & van den Brandt, [1]). Over the past four decades, Zeegers et al. write many epidemiological studies suggest that urothelial cancers are influenced by environmental factors, including tobacco smoking, fluid intake, exposures to industrial chemicals, and diet.

Smoking is certainly an established risk factor for urothelial cancer, and high intake of vegetables or fruits are believed to reduce the risk of urothelial cancer (Sakauchi et al., [2]).

This study will contribute to people's understanding of the importance of a daily intake of green leafy vegetables (GLV), including cruciferous vegetables (CV). GLV come from a wide variety of plants all over the world, and nearly one thousand species of plants with edible leaves are known. GLV most often come from short-lived herbaceous plants such as lettuce and spinach. CV are mostly green leafy vegetables from the family Cruciferae that are widely cultivated, with many genera, species, and cultivars being raised for food production. Examples are cauliflower, cabbage, cress, bok choy, broccoli, kale, collard greens and similar green leafy vegetables and their roots. Studies indicate long-term intake of GLV and the micronutrients they contain may reduce risk of Type 2 diabetes, CVD and some types of cancers (Carter, Gray, Troughton, Khunti, & Davies, [3]; Joshipura et al., [4]; Smith-Warner et al., [5]). 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 urothelial cancers.

The research hypothesis of this study is the consumption of green leafy vegetables (GLV) including cruciferous vegetables (CV) will significantly reduce the incidence of urothelial cancers. There is a need to research peer-reviewed journals to investigate casecontrol studies, prospective cohort studies, and comparative studies dealing with GLV intake and the incidence of these horrific 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.

showing no severe methodological flaws; (4) the collection of primary studies had to be a collaborative cohort, case-control, population-based cohort, or a prospective cohort study design; (5) those including relations between similar independent variables (GLV intake levels including CV) and dependent variables (incidence of urothelial cancer); (6) all studies had to measure GLV consumption, which was estimated by highest versus lowest quantiles (quintiles, or quartiles, or tertiles); (7) those that reported an effect size of: odds ratio (OR), or risk ratio (RR), or hazard ratio (HR), and their respective 95% confidence intervals (CI) data; and (8) 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 (HR, OR, RR, 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 metaanalysis. CMA v.2 was also used to create a highresolution 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.Separate meta-analyses were calculated for each effect size, because OR, RR, or HR, cannot be converted into each other.

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 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 urothelial 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., [6]). 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., [6]). The conventional value of significance level for this meta-analysis was pre-set to an alpha of 0.05 **??**Stigler,[7]).

2 III. Results

Over a two-year search period (2012-2015), thousands of scientific papers were reviewed for this meta-analysis. Table 1 shows the total number of collected studies (N=13) that were relevant and reviewed in this meta-analysis. Four studies were combined in meta-analysis that examined the relationship between GLV intake and the incidence of urothelial cancer and used HR as the effect size. Three studies were combined that included the relationship between GLV intake and incidence of urothelial cancer and used RR as the effect size. Six case-control studies were combined that included the relations between GLV intake and the incidence urothelial cancer and used OR as the effect size.

3 a) Research Question

Does an increased intake of GLV significantly reduce incidence of urothelial cancer?

4 b) Urothelial Cancer ——OR

Six studies met the inclusion criteria that investigated the relationship between the incidences of urothelial cancer with the intake of GLV. The six studies shown had a similar common effect size (OR), and a meta-analysis was used to combine results from the six different studies. Figure 1 shows a Forest plot of the six studies and meta-analysis. The random effect model was selected for combining the source studies. The random effect model indicates an overall OR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on urothelial cancer as: OR = 0.749 (95% CI .678 to .827), $p<.001$. Note: In the Grieb et al. [8] study, Hsu et al. [9] study, and the Wakai et al. [10] study, OR results for subgroups GLV and CV were combined to calculate one treatment effect for eachVolume XVI Issue V Version I Year 2016 (D D D D) F

The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta-Analysis source study. Also, the Hu et al. [11] study combined 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, and CV. In this study, it emerged that the effect sizes were comparable for each subgroup, so it was decided to use the study as the unit of analysis. This required calculating a "combined" effect size (utilizing the CMA v.2 software) for subgroups within each study, and imputes the values for the full group, which recorded one treatment effect 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). Begg and Mazumdar's test for correlation, Egger's test for regression, Duval and Tweedie's trim

and fill, and the classic fail-safe method were also calculated by CMA v.2 software for detecting the presence of publication bias and assessing its impact on this meta-analysis study.

(Higgins, Hedges, Borenstein, & Rothstein, [6]). An effect value to >.05. The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta-Analysis male, female, GLV, and CV results to calculate one treatment effect for each source study. Brock et al. [12], and Zhao et al. [13] did not combine variables in their studies.

5 c) Detecting the Presence of Publication Bias—OR

All the collected studies were evaluated for the likelihood of publication bias using a funnel plot of the log odds ratio versus its precision (1/standard error), Begg and Mazumdar's test for correlation, Egger's test for regression, Duval and Tweedie's trim and fill, and Classic fail-safe method. Note in Supplementary Figure 1 that the large urothelial cancer studies appear toward the top of the funnel plot graph, and tend to cluster near the mean of the log OR in the relationship between six urothelial cancer 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 OR. Supplementary Figure 1 shows a possible presence of publication bias in the six studies with the studies distributed asymmetrically about the mean effect size. By contrast, in the absence of publication bias, the bottom of the funnel plot would tend to show an even concentration of studies around the mean (Borenstein et al., [14]). Duval and Tweedie's method imputes two missing studies to the right and adjusts new OR= 0.757, 95% CI = 0.688 to 0.834 from the observed values (0.749, 95% CI = 0.678 to 0.827). Begg and Mazumdar's rank correlation p-value (2-tailed) = .35, indicating no evidence of publication bias. Egger's linear regression p-value (2-tailed) = .38, also indicating no evidence of publication bias. Classic fail-safe N test imputes there would be 41 missing studies that would bring the p-

6 d) Urothelial Cancer ————HR

Four studies met the inclusion criteria that investigated the relationship between the incidences of urothelial cancer with the intake of GLV. The four studies shown had a similar common effect size (HR) and a meta-analysis was used to combine results from the four different studies. Figure 2 shows a Forest plot of the four studies and meta-analysis. The random effect model was selected for combining the source studies. This model indicates an overall HR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on incidence of urothelial cancer as: HR = 0.803 (95% CI .699 to .922), p=.002. Note: In the Park et al. [15] study, HR results for subgroups GLV, CV, male, and female were combined to calculate one treatment effect for each source study. Sakauchi et al. [16], Ros et al. [17], and Tang et al. [18] did not combine variables in their studies.

7 e) Detecting the Presence of Publication Bias——HR

Supplementary Figure 2 shows no evidence of publication bias in the four studies, with the studies distributed symmetrically about the mean effect size. Duval and Tweedie's method imputes missing studies to the right and adjusts new HR = 0.805, 95% CI = 0.703 to 0.922 from the observed values (0.803, 95% CI = 0.699 to 0.922). Begg and Mazumdar's rank correlation p-value (2-tailed) = 1.00, indicating no evidence of publication bias. Egger's linear regression p-value (2tailed) = .679, also indicating no evidence of publication bias. Classic fail-safe N test imputes there would be 4 missing studies that would bring the p-value to >.05.

8 f) Urothelial Cancer ————RR

Three studies met the inclusion criteria that investigated the relationship between the incidences of urothelial cancer with the intake of GLV. The three studies shown had a similar common effect size (RR), and a meta-analysis was used to combine results from the three different studies. Figure 3 shows a Forest plot of the studies and meta-analysis. The random effect model was selected for combining the source studies. This indicates an overall RR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on incidence of urothelial cancer as: RR = 0.896 (95% CI .691 to 1.16), p=.405. Note: In the Zeegers et al. [19] study, RR results for subgroups cooked GLV and raw GLV were combined to calculate one treatment effect for each source study. In the Michaud et al. [20] study, GLV and CV were combined to calculate one treatment effect for this source study. Michaud et al. [21] did not combine variables in their study.

9 g) Detecting the Presence of Publication Bias——RR

Supplemental Figure 3 shows no evidence of publication bias in the three studies, with the studies distributed symmetrically about the mean effect size. Duval and Tweedie's method imputes zero missing studies to the right and calculates no adjusts of RR = 0.896, 95% CI = 0.691 to 1.160 from the observed values (0.896, 95% CI = 0.691 to 1.160). Begg and Mazumdar's rank correlation p-value (2-tailed) = 0.602, indicating no evidence of publication bias. Egger's linear regression p-value (2-tailed) = 0.967, also indicating no evidence of publication bias. Classic failsafe N test imputes there would be 0 missing studies that would bring the p-value to >.05.

10 IV. Discussion of Findings

The intent of this study was to investigate potential influences of GLV intake on incidences of urothelial cancer worldwide. An extensive search for relevant studies was initiated to learn more about these diet-disease relationships. Only 13 studies were collected and used in three separate meta-analysis. However, this meta-analysis study included 979,363 total participants collected from the 13 source studies. The research questions in this meta-analysis study was; does an increased intake of GLV significantly reduce the Volume XVI Issue V Version IYear 2016 (D D D D) F

The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta-Analysis worldwide incidence of urothelial cancers studied? Even after adjusting effect sizes for possible publication bias via Duval and Tweedie's method, all three metaanalysis results indicated GLV consumption reduced urothelial cancer incidences, and two of the three metaanalysis results were significant. Six case-control studies were collected that investigated the relationship between the incidences of urothelial cancers with the consumption of GLV and used OR as their effect size. These studies included 14,194 case participants and controls, with 3,823 case participants having urothelial 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 = 0.749 (95% CI .678 to .827), p<.001, showing 25.1% lower odds that an intake of GLV significantly reduces the incidence of urothelial cancers in the highest intake category as compared with the lowest. Just four prospective cohort studies were collected that investigated the relationship between the incidences of urothelial cancers with the consumption of GLV and used HR as their effect size. However, these four studies included 769,297 participants with 1,855 diagnosed with urothelial cancers. The random effect model indicated an overall HR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on cancer as: HR = 0.803 (95% CI .699 to .922), p=.002, which indicated an increased intake of GLV significantly reduces the incidences of urothelial cancers by 19.7%. Just three worldwide prospective cohort studies were collected that investigated the relationship between the incidences of urothelial cancers with the consumption of GLV and used RR as their effect size. However, these three studies included 195,872 participants with 1,134 cases with urothelial cancer. The random effect model indicated an overall RR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on cancer as: RR = 0.896 (95% CI .691 to 1.160), p=.405. The RR results indicate that increased GLV intake non-significantly reduces the incidence of these urothelial cancers by 10.4%.

11 a) Phytochemicals in GLV Reduce Incidence of Diseases

Cancer is a group of more than 100 different types of malignancies, and there are several potential substances in GLV that my exhibit anticancer effects (Rajalakshmi & Agalyaa, [22]). 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, [23]). Vitamin K has also been shown to inhibit the growth of mammalian tumor cells in culture (Prasad, Edwards-Prasad, & Sakamoto, [24]). Also, GLV are high in carotenoids such as beta-carotene, and in animal experiments they were shown to suppress liver carcinogenesis (Moreno et al., [25]). Carotenoids found in GLV have antioxidant potential in the scavenging of harmful free radicals **??**Krinsky,[26]) and they appear to play an important role in the prevention of hepatitis virusrelated liver carcinogensis (Kurahashi et al., [27]). Also, due to the potent anti-proliferative effects of isothiocyanates on bladder cancer in in vitro and in vivo experiments, CV consumption may play a role in survival among patients with bladder cancer (Tang et al., [18]). In the 2010 decade, researchers are conducting extensive research studies to discover phytochemicals connections to disease prevention, but so far, solid evidence is mostly lacking (DeBruyne, Pinna, & Whitney, [28]). There are thousands of these phytochemicals in GLV and researchers are just beginning to understand and theorize how a handful of these phytochemicals work to reduce incidence of cancer and other diseases, and what is current in the 2010 decade may change tomorrow (DeBruyne, Pinna, & Whitney, [28]).

12 V. Acknowledgements

IRB at Trident University International ethically approved the content of this meta-analysis (no human subjects used). No conflict of interests are declared with this research, and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Theory and editing were improved in this paper by my dissertation committee which included Dr Mickey Shachar, Dr Frank Gomez, and Dr Kyung-Ae Son-Guidry. Volume XVI Issue V Version I [1]

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Study N

Figure 1: Table 1 :

Year 2016 Study name	Subgroup within study	Statistics for each study			Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Brock et al. (2012)	CV 0.800	0.527	1.215	0.296	5.62
Grieb et al. (2009)	Combined 0.573	0.297	1.104	0.096	2.28
Hsu et al. (2007)	Combined 0.837	0.709	0.990	0.037	35.19
Hu et al. (2003)	Combined 0.703	0.593	0.834	0.000	33.79
Wakai et al. (2004)	Combined 0.649	0.377	1.116	0.118	3.34
Zhao et al. (2007)	CV 0.710	0.568	0.887	0.003	19.78
Radom effect model	0.749	0.678	0.827	0.000	
D D D D) F (	0.1 0.2 0Hazard	Lower	Upper ratio limit	limit	p-Value Relative weight
Park et al. (2013)	Combined 0.798	0.664	0.958	0.016	57.37
Ros et al. (2012)	GLV 0.800	0.621	1.031	0.085	29.88
Sakauchi et al. (2004) GLV	0.760	0.419	1.378	0.366	5.44
Tang et al. (2010)	CV 0.890	0.533	1.487	0.656	7.30

Figure 2: .5 1 2 5 10 Study name Subgroup within study Statistics for each study Hazard ratio and 95% CI

	Risk ratio	Lower limit	Upper limit	p-Value	Relative weight
Zeegers et al. (2001) Combined	0.920	0.753	1.124	0.414	40.76
Michaud et al. (1999) Combined	0.681	0.500	0.929	0.015	30.36
Michaud et al. (2002) CV Men	1.150	0.828	1.597	0.404	28.88
Random effect model	0. 896	0.691	1.160	0.405	

[Note: 0.1 0.2 0.5 1 2]

Figure 3: Random effect model 0.803 0.699 0.922 0.002 0.10.2 0.5 1 2 5 10 Study name Subgroup within study Statistics for each study Risk ratio and 95% CI

Supplementary Figure **??**: Funnel plot showing six studies with four studies on the left of mean log odds ratio and two on the right signifying possible presence of publication bias.

Supplementary Figure **??**: Funnel plot showing four studies with one study on the left of mean log hazard ratio and one on the right signifying possible absence of publication bias.

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