Evaluation of the effect of dietary vegetable consumption on reducing risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers

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Objective—To evaluate the effects of vegetable consumption and vitamin supplementation on the risk of developing transitional cell carcinoma (TCC) of the urinary bladder in Scottish Terriers.

Design—Case-control study.

Animals—92 adult Scottish Terriers with TCC (cases) and 83 Scottish Terriers with other conditions (controls).

Procedure—Owners of dogs with TCC completed a questionnaire regarding their dogs' diet and intake of vitamin supplements in the year prior to diagnosis of TCC; owners of control dogs completed the questionnaire for a comparable time period. The risk (odds ratio [OR]) of developing TCC associated with diet and vitamin supplementation was determined by use of logistic regression.

Results—After adjustment for age, weight, neuter status, and coat color, there was an inverse association between consumption of vegetables at least 3 times/wk (OR, 0.30; 95% confidence interval [CI], 0.15 to 0.62) and risk of developing TCC. For individual vegetable types, the risk of developing TCC was inversely associated with consumption of green leafy vegetables (OR, 0.12; 95% CI, 0.01 to 0.97) and yellow-orange vegetables (OR, 0.31; 95% CI, 0.14 to 0.70). Consumption of cruciferous vegetables was not significantly associated with a similar reduction in risk of developing TCC (OR, 0.22; CI, 0.04 to 1.11). The power of the study to detect a 50% reduction in TCC risk associated with daily vitamin supplementation was considered low (25%).

Conclusions and Clinical Relevance—Results suggest that consumption of certain vegetables may prevent or slow the development of TCC in Scottish Terriers. (*J Am Vet Med Assoc* 2005;227:94–100)

Malignant neoplasia is the leading cause of death in several breeds of dogs, including the Golden Retriever, Flat-Coated Retriever, Rottweiler, and Boxer.[1,2] A survey conducted in 1968 revealed that the incidence rate of malignant neoplasm in dogs exceeded the incidence rate in humans.[3] As the longevity of companion animals increases, the incidence and mortality rate from malignancies are expected to increase.

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Transitional cell carcinoma (TCC) of the urinary bladder accounts for approximately 2% of all neoplasms diagnosed in dogs and humans.[4,5] An increasing frequency of TCC over time has been reported for both species.[4,6] Transitional cell carcinoma is usually diagnosed in humans ≥ 65 years of age, whereas in dogs, the mean age at diagnosis is 11 years (approx human equivalent, 60 years).[4,7] Transitional cell carcinoma in dogs is similar to the disease in humans with regard to histologic characteristics, molecular features, biological behavior, response to medical treatment, and prognosis.[4] In humans, increased risk of TCC has been associated with urban dwelling, cigarette smoking, and exposure to benzene and polycyclic aromatic hydrocarbons.[6] In dogs, increased risk has been associated with certain breeds (eg, Scottish Terrier and West Highland White Terrier), female sex, overweight or obese body condition, urban dwelling, exposure to insecticides containing benzene or other supposed inert ingredients, and herbicides.[8-10] Twenty percent of dogs and 5% to 20% of humans with invasive TCC had metastasis at the time of diagnosis.[4,11] Invasive (intermediate to high-grade) TCC results in metastasis of the primary tumor to secondary sites in approximately 50% of affected dogs and humans.[4] Chemotherapy is only partially effective for metastatic TCC, and most humans and dogs with metastatic TCC die from the disease.[4,11]

There is conflicting evidence regarding an association between risk of TCC and vegetable consumption in humans. Results of previous epidemiologic studies[12-19] of bladder cancer have suggested a 20% to 60% reduction in risk for the highest versus lowest level of vegetable consumption in humans. However, not all studies[20-23] have detected a protective effect for vegetable consumption in bladder cancer, and there is a lack of consensus regarding which vegetables are beneficial.[12-19] For example, in some studies,[12-18] regular consumption of green or yellow vegetables was associated with a 40% to 60% decrease in risk of bladder cancer, an effect attributed to the high content of vitamin A or lutein in those vegetables. Other studies[22,23] did not reveal a reduction in risk of bladder cancer associated with consumption of specific vegetables or carotenoids. In 1 study,[19] dietary intake of cruciferous vegetables such as broccoli and cabbage, but not cauliflower, kale, or brussels sprouts, was associated with reduced risk of bladder cancer; a similar effect has been reported[24-28] for vitamins A, C, and E. A decreased risk of bladder cancer has been reported in humans in association with regular consumption of vitamin C[24,26] or regular and long-term consumption of vitamin E.[27,28]

The objective of the study reported here was to evaluate the pattern (frequency and amount) of vegetable consumption and vitamin supplementation in Scottish Terriers in relation to the risk of developing TCC. The hypothesis tested was that frequent consumption of vegetables or dietary supplementation with vitamins A, C, or E is associated with a decreased risk of developing TCC in Scottish Terriers.

Materials and Methods

Study design—Beginning in June 2001, owners of Scottish Terriers with TCC (cases) and Scottish Terriers with other health problems, including other neoplasias (controls), were recruited through Web sites of the Scottish Terrier Club of America and the Purdue Comparative Oncology Program. Details of the methods have been published.[10,29] The specific study hypothesis was not revealed to the participants or recruiters.

Cases and controls—Dogs eligible for the study were Scottish Terriers with a diagnosis of TCC made after January 1, 1995, and for which the owner had written proof of the diagnosis in the form of a histopathology report, cytology report, or both. Cases in which the diagnosis was made on the basis of results of histologic assessment of biopsy specimens were designated as confirmed, whereas cases with cytology reports alone were considered as presumptive. Only 1 dog/household was included if the owner had more than 1 dog with TCC. Control dogs were Scottish Terriers older than 6 years of age on or after July 1, 1995, and without a diagnosis of TCC. Dogs with a history of urinary tract disease in the 2 years preceding the study or preceding death were excluded from inclusion in the study as controls because clinical signs of urinary tract disease often precede a diagnosis of TCC. Only 1 dog/household could serve as a control, and control dogs could not come from the same household as a case dog. All cases and controls recruited by August 1, 2003, were included in the analyses.

Dietary assessment—Owners of case and control dogs completed a written questionnaire pertaining to the dogs' diets 1 year prior to diagnosis for the case dogs and 1 year prior to enrollment into the study, or prior to death if deceased, for control dogs. On the basis of a typical daily feeding schedule, owners indicated the percentage by volume of different types of food consumed by their dogs, including commercial dog foods (eg, dry, canned, semimoist, and unprocessed) as well as home-prepared foods and table scraps. If home-prepared foods or table scraps were fed, owners indicated specific food items or ingredients from a list provided to them. In addition, owners were asked the number of times per week each food was fed, the amount fed at each feeding, and the number of years each food item had been fed. Foods such as meats, eggs, fish, dairy products, oils and fats, carbohydrates and starches, vegetables, and fruit were on the list provided to owners for use in answering the questionnaire. Additional space was provided for owners to indicate other foods fed. Methods of food preparation were not assessed.

Dogs were grouped by how often they consumed the following vegetables: green beans, broccoli, cabbage, cauliflower, brussels sprouts, carrots, corn, peas, celery, various squashes, cucumbers, zucchini, sweet potatoes, spinach, kale, turnip or mustard greens, iceberg or head lettuce, romaine or leaf lettuce, green peppers, garlic (fresh or powdered), and tomatoes. Vegetables were grouped as yellow-orange (ie, carrots, sweet potatoes, and yellow squash), green leafy (ie, spinach, mustard and turnip greens, romaine and leaf lettuce), or cruciferous (ie, broccoli, cabbage, cauliflower, brussels sprouts, and kale). These groupings reflect vegetables with a high content of certain phytochemicals thought to influence the risk of neoplasia. For example, yellow-orange vegetables contain high concentrations of β-carotene, green leafy vegetables contain high concentrations of lutein, and cruciferous vegetables contain high concentrations of glucosinolates. Vegetables that were not included in any of the above 3 groups were grouped as other (ie, tomato, peas, beans, asparagus, celery, cucumbers, bell peppers, radish, turnip, corn, and garlic). The total number of servings of vegetables consumed per week for each dog was calculated. Although the questions were designed to estimate the amount of vegetables consumed per serving, owner responses to these questions were inadequate for statistical analyses.

Assessment of dietary supplements—Information was collected on the type, frequency, and amount of vitamins and minerals, chondroprotective compounds, and supplements for skin or coat health administered to the dog. Such information included the administration of multivitamins, a combination of vitamin A and β-carotene, vitamin C, and vitamin E.

Statistical analyses—Data were entered and analyzed by use of analytic software.[30,a] Descriptive data were compared for cases and controls by use of the χ^2 test for categoric variables and the independent sample *t* test for normally distributed continuous variables. Each potential risk factor was examined for an association with TCC by use of univariate logistic regression.[31,32,b] The association of potential risk factors with TCC was expressed as an **odds ratio (OR)** with a 95% **confidence interval (CI)**. The OR in a case-control study represents the risk of disease among dogs with an inherent factor (eg, female sex) or among dogs exposed to a specific environmental factor (eg, a specific vegetable group), compared with those lacking the same inherent factor or exposure. An OR > 1.0 indicates an increased risk of disease, whereas an OR < 1.0 indicates a decreased risk. If the 95% CI of the OR excluded 1.0, the association between the factor and risk of TCC was considered significant at $P < 0.05$.

Multivariate logistic regression was used to model the risk of TCC for potential host and dietary risk factors with $P < 0.10$ in univariate analysis. Separate multivariate models were built when potential risk factors were highly correlated. For example, many dogs that consumed green leafy vegetables also consumed yellow-orange vegetables, making it impossible to calculate stable risk estimates for each vegetable type in the same model. Therefore, the OR associated with each vegetable type was adjusted for host risk factors included in the model but not for the consumption of other types of vegetables. Regression diagnostic tests were used to evaluate adequacy of the fit of final multivariate models.[33]

Results

Study population—Ninety-two cases and 83 controls were enrolled in the study. Fifty-six (60.9%) case dogs and 10 (12.0%) control dogs were deceased at the time of enrollment. Seventy (76.1%) case dogs had a diagnosis of TCC confirmed via histologic analysis, whereas in 22 (23.9%) case dogs, the diagnosis was made on the basis of cytologic assessment of a needle aspirate sample (13 dogs), urine sample (11), or bladder wash sample (1). For 6 of those 22 dogs, diagnostic imaging was performed in addition to cytologic evaluation. Twenty-nine (31.5%) case dogs had clinical signs compatible with urinary tract disease in the 2-year period prior to the diagnosis of TCC, a finding consistent with development of TCC. The most com-

mon disease conditions affecting control dogs were neoplastic diseases other than TCC (20/83 dogs [24.1%]), skin disease (18 [21.7%]), parasitic infections (16 [19.3%]), idiopathic increase in serum activity of liver enzymes (13 [15.7%]), or scottie cramp (a heritable neurologic disorder; 6 [7.2%]). Four (4.8%) control dogs had a history of urinary tract disease that was treated successfully 2 to 5 years prior to entry into the study; those dogs were included as controls because the absence of urinary tract disease for at least 2 years prior to the study made latent TCC unlikely.

The mean ± SD age for case and control dogs was 9.9 ± 1.9 years and 9.1 ± 2.3 years, respectively (P = 0.02); the median ages were 9.8 years (range, 4.8 to 15.1) and 8.5 years (range, 6.0 to 14.1), respectively. The mean ± SD weight for case and control dogs was 11.2 ± 2.4 kg (24.6 ± 5.28 lb) and 10.7 ± 1.7 kg (23.5 ± 3.74 lb), respectively (P = 0.09).

Thirty-six (39.1%) cases and 35 (42.2%) controls were male. Eighty-six (93.5%) case dogs and 69 (83.1 %) control dogs were neutered (P = 0.04). Twenty-five (27.2%) cases and 35 (42.2%) controls had a nonblack coat color (P = 0.04). One hundred fifty-five dogs (88.6%) were registered with the American Kennel Club.

Diet—Cases and controls were not significantly different regarding the food types consumed daily (P > 0.10). Dry commercial dog food was the predominant food type fed daily to > 95% of the dogs in the study. Only 5 dogs (4 controls and 1 case) did not receive any dry food. Dry food comprised > 50% by volume of the total diet for 77 (83.7%) case dogs and 70 (84.3%) control dogs (P = 0.91). Three dogs (all controls) consumed diets consisting solely of home-prepared foods or table scraps (ie, 100% by volume of total diet). Home-prepared foods or table scraps comprised > 50% by volume of the total diet for 2 (2.2%) case dogs and 4 (4.8%) control dogs (P = 0.34). The mean ± SD number of years during which dogs were maintained on their reported diets was 7.9 ± 3.1.

Sixty-six (71.7%) case dogs and 52 (62.7%) control dogs received home-prepared foods or table scraps (P = 0.20). In terms of home-prepared foods or table scraps, the proportions of case versus control dogs that had consumed meat or meat products, fish, eggs, dairy products including yogurt, oils and fats, carbohydrates and starches, fruit, and vegetables at any time were not significantly different (P > 0.10). Fewer case dogs than control dogs consumed vegetables on a weekly basis (46.7% and 55%, respectively; P = 0.25; **Table 1**).

Table 1—Frequency of vegetable consumption by 92 Scottish Terriers with transitional cell carcinoma (TCC) of the urinary bladder (cases) and 83 Scottish Terriers without TCC (controls).

	Frequency of consumption											
	Consumed at least once				At least once per week				At least 3 times/wk			
	Cases		Controls		Cases		Controls		Cases		Controls	
Type of vegetable consumed	No.*	%	No.*	%	No.*	%	No.*	%	No.*	%	No.*	%
None	35	38.0	31	37.4	49	53.3	37	44.6	69	75.0	47	56.6
Any	57	62.0	52	62.7	43	46.7	46	55.4	23	25.0	36	43.4
Any cruciferous vegetables	20	21.7	20	24.1	12	13.0	16	19.3	2	2.2	8	9.6
Broccoli	18	19.6	19	22.9	11	12.0	14	16.9	1	1.1	5	6.0
Cauliflower	10	10.9	9	10.8	6	6.5	6	7.2	0	0.0	4	4.8
Cabbage	10	10.9	8	9.6	4	4.4	7	8.4	0	0.0	3	3.6
Kale	0	0.0	3	3.6	0	0.0	3	3.6	0	0.0	3	3.6
Brussels sprouts	2	2.2	1	1.2	2	2.2	0	0.0	1	1.1	0	0.0
Any green leafy vegetable	15	16.3	15	18.1	8	8.7	13	15.7	1	1.1	8	9.6
Lettuce (all types)	8	8.7	10	12.0	6	6.5	8	9.6	1	1.1	4	4.8
Salad greens	2	2.2	0	0.0	2	2.2	0	0.0	0	0.0	0	0.0
Spinach	0	0.0	5	6.0	0	0.0	3	3.6	0	0.0	3	3.6
Collard greens	0	0.0	1	1.2	0	0.0	1	1.2	0	0.0	1	1.2
Herb (parsley)	0	0.0	2	2.4	0	0.0	2	2.4	0	0.0	2	2.4
Unspecified/missing	5	5.4	1	1.2	0	0.0	1	1.2	0	0.0	0	0.0
Any yellow-orange vegetable	45	48.9	42	50.6	31	33.7	34	41.0	14	15.2	26	31.3
Carrots	41	44.6	40	48.2	30	32.6	33	39.8	13	14.1	25	30.1
Pumpkin/squash	12	13.0	8	9.6	6	6.5	6	7.2	2	2.2	3	3.6
Sweet potato	9	9.8	6	7.2	3	3.3	5	6.0	0	0.0	3	3.6
Any other vegetable	34	37.0	37	44.6	22	23.9	28	33.7	15	16.3	20	24.1
Tomato	11	12.0	9	10.8	3	3.3	5	6.0	2	2.2	2	2.4
Peas	6	6.5	3	3.6	5	5.4	2	2.4	1	1.1	0	0.0
Green beans	12	13.0	15	18.1	6	6.5	12	14.5	3	3.3	9	10.8
Asparagus	1	1.1	1	1.1	1	1.1	1	1.2	1	1.1	1	1.2
Celery	1	1.1	2	2.4	1	1.1	2	2.4	1	1.1	1	1.2
Cucumbers	3	3.3	2	2.4	3	3.3	2	2.4	3	3.3	2	2.4
Bell peppers (green, red)	1	1.1	4	4.8	1	1.1	4	4.8	1	1.1	4	4.8
Radish, turnip	1	1.1	1	1.2	1	1.1	1	1.2	1	1.1	1	1.2
Corn	0	0.0	1	1.2	0	0.0	1	1.2	0	0.0	1	1.2
Beans (kidney, lima)	0	0.0	2	2.4	0	0.0	2	2.4	0	0.0	2	2.4
Garlic	19	20.7	16	19.3	13	14.1	14	16.9	11	12.0	11	13.3

*Number of case and control dogs consuming individual vegetable types may not total 100% because a dog may have consumed more than 1 vegetable type.

However, there was a significant ($P = 0.01$) difference in the proportion of case and control dogs fed vegetables ≥ 3 times/wk (25% and 43.4%, respectively). The most frequently consumed vegetables were those in the yellow-orange group.

Vitamin supplements—Sixty-seven of 175 (38.3%) dogs received vitamin supplements at least once per week; most dogs received a vitamin supplement daily. Case and control dogs did not differ significantly with respect to vitamin supplementation on a weekly (34.8% and 42.2%, respectively; $P = 0.32$) or daily (28.3% and 34.9%, respectively; $P = 0.34$) basis (**Table 2**). Also, there were no differences between the groups regarding the type of vitamin supplementation. None of the cases or controls received daily vitamin A or β-carotene supplements.

Univariate analysis—Consumption of any type of vegetable at least 3 times/wk was associated with a significantly (OR, 0.44; 95% CI, 0.23 to 0.83; $P = 0.01$) decreased risk of developing TCC. Specifically, consumption of green leafy vegetables (OR, 0.10; 95% CI, 0.01 to 0.84; $P = 0.03$) and yellow-orange vegetables (OR, 0.39; 95% CI, 0.19 to 0.82; $P = 0.01$) at least 3 times/wk was associated with a significantly decreased risk of developing TCC, whereas consumption of cruciferous vegetables at least 3 times/wk yielded a P value of 0.05, but the 95% CI included 1.0 (OR, 0.21; 95% CI, 0.04 to 1.01; $P = 0.05$). Daily administration of multivitamins (OR, 0.73; 95% CI, 0.36 to 1.49; $P = 0.87$), vitamin C (OR, 0.47; 95% CI, 0.15 to 1.47; $P = 0.20$), or vitamin E (OR, 0.49; 95% CI, 0.14 to 1.75; $P = 0.27$) was also associated with a decreased risk of developing TCC, although the decrease in risk was not significant.

Multivariate analysis—Separate multivariate logistic regression models were constructed for each vegetable type with either confirmed cases alone or both confirmed and presumptive cases. Because the observed pattern of risk of TCC was similar between these 2 models, only models with all cases combined were evaluated (**Table 3**). Because age, weight, neuter status, and coat color were unequally distributed between case and control dogs, these host factors were included in all multivariate models.

Among host factors, increasing age (OR, 1.25; 95% CI, 1.07 to 1.47; $P = 0.006$) and sexually neutered state (OR, 3.57; 95% CI, 1.13 to 11.31; $P = 0.03$) were significantly associated with increased risk of developing TCC, whereas increased body weight was not (OR, 1.14; 95% CI, 0.96 to 1.34; $P = 0.13$). Nonblack coat color (OR, 0.42; 95% CI, 0.20 to 0.86; $P = 0.02$) was significantly associated with a decreased risk of developing TCC. Consumption of any vegetable type at least 3 times/wk (OR, 0.30; 95% CI, 0.15 to 0.62; $P = 0.001$) was significantly associated with a decreased risk of developing TCC after adjustment for host risk factors.

For the individual types of vegetables consumed, the reduction in risk associated with consumption of green leafy (OR, 0.12; 95% CI, 0.01 to 0.97; $P = 0.05$) and yellow-orange (OR, 0.31; 95% CI, 0.14 to 0.70; $P = 0.005$) vegetables was significant after adjustment for host risk factors, whereas the risk for developing TCC

Table 2—Frequency of vitamin supplementation for 92 Scottish Terriers with TCC (cases) and 83 Scottish Terriers without TCC (controls).

	At least once per week				At least once per day			
	Cases		Controls		Cases		Controls	
Type of vitamin supplementation	No.*	%	No.*	%	No.*	%	No.*	%
None	60	65.2	48	57.8	66	71.7	54	65.1
Any vitamin	32	34.8	35	42.2	26	28.3	29	34.9
Multivitamins	30	32.6	30	36.1	23	25.0	26	31.3
Vitamin C	5	5.4	10	12.1	5	5.4	9	10.8
Vitamin E	5	5.4	8	9.6	4	4.4	7	8.4
Vitamin A /β-carotene	0	0.0	1	1.2	0	0.0	0	0.0

*Sum of the number of cases and controls with vitamin supplementation may not total 100% because a dog may have received more than 1 type of vitamin supplement.

Table 3—Vegetables consumed at least 3 times/wk and the risk of TCC of the urinary bladder in 87 case and 82 control Scottish Terriers.

Model*	Type of vegetables consumed ≥ 3 times/wk† (yes vs no‡)	Odds ratio§	95% confidence interval	*P* value	Percentage reduction in risk
1	All types**	0.30	0.15, 0.62	0.001	70
2	Cruciferous	0.22	0.04, 1.11	0.07	78
3	Green leafy	0.12	0.01, 0.97	0.05	88
4	Yellow-orange	0.31	0.14, 0.70	0.005	69

*A separate model was built for each type of vegetable consumed. †The pattern of diet pertains to 1 year prior to diagnosis of TCC for cases and a comparable time period for controls. ‡No = Consumption of vegetable types < 3 times/wk. §The odds ratio associated with each vegetable type was adjusted for the same host factors, including age, weight, neuter status, and color of coat, but was not adjusted for the other vegetable groups, because of collinearity. **Includes cruciferous, green leafy, yellow-orange, and other vegetables (eg, tomatoes, green beans, green peppers, celery, and peas).

associated with consumption of cruciferous vegetables was decreased but not significant (OR, 0.22; 95% CI, 0.04 to 1.11; $P = 0.07$).

A dose-response relationship between an increased number of servings of all vegetables combined and a decreased risk of developing TCC was observed among dogs that consumed vegetables on a weekly basis. For example, compared with dogs that consumed < 7 servings of vegetables/wk (OR, 1.00), dogs that consumed 7 to 13 servings/wk (OR, 0.31; 95% CI, 0.13 to 0.77; $P = 0.01$) and dogs that consumed ≥ 14 servings/wk (OR, 0.26; 95% CI, 0.09 to 0.72; $P = 0.01$) had a significantly decreased risk of developing TCC (P for trend, 0.01) after adjustment for host risk factors.

Discussion

Approximately 50% of the dogs in this study consumed vegetables on a weekly basis. The vegetable fed most frequently was carrots. This may be related to the fact that owners frequently reported using small carrots as treats or rewards. This pattern of vegetable consumption, however, may not be comparable for larger dogs. The data indicate that consumption of any type of vegetable ≥ 3 times/wk was associated with a 70% reduction in risk of developing TCC in Scottish Terriers. Consumption of yellow-orange vegetables or green leafy vegetables ≥ 3 times/wk was associated with an approximately 70% and 90% reduction in risk of developing TCC, respectively. Because of the high correlation in consumption patterns for specific vegetables (ie, dogs that consumed 1 type of vegetable were more likely to consume another type), it was not possible to measure the risk of developing TCC against dogs' consumption of individual vegetable types.

It has been suggested that anticarcinogenic substances such as carotenoids, ascorbate, tocopherols, selenium, dietary fiber, dithiolthiones, isothiocyanates, indoles, phenols, protease inhibitors, allium compounds, plant sterols, and limonene in vegetables can slow progression or prevent initiation of neoplasms.[34] These anticarcinogenic substances in plants are collectively known as phytochemicals or bioactive compounds[34] and may have complementary or overlapping mechanisms of action, including modulation of carcinogen detoxification enzymes, scavenging of cancer-inducing oxidative agents, stimulation of the immune system, regulation of gene expression in cell proliferation and apoptosis, hormone metabolism, and antibacterial and antiviral effects.[35] Whole foods are considered to provide more health benefits than purified isolated phytochemical compounds or dietary supplements.[35]

Results of a recent study[36]of bladder cancer in humans suggest that consumption of vegetables (all types combined) had a protective effect against the development of bladder cancer via inhibition of the formation of DNA adducts. Adducts of DNA are formed when genotoxic carcinogens react with DNA bases and reflect an enhanced risk of developing a mutation-related disease.[37]

Several epidemiologic studies[12-18,38] in humans provide evidence for the importance of green and yellow vegetables in reducing the risk of developing TCC. In 1 study[17] of a high-risk cohort (survivors of the atomic bomb in Japan), consumption of green and yellow vegetables had a dose-response relationship with the risk of developing bladder cancer—the higher the frequency of consumption, the lower the risk. Other studies[12,13,16] report a significantly decreased risk of developing bladder cancer with increased frequency and amount of consumption of individual vegetables such as carrots and spinach.

Two of the most important components of green and yellow vegetables are carotenoid (provitamin A) and retinol (preformed vitamin A). Naturally occurring preformed vitamin A includes the compounds retinol and its esters (retinaldehyde and retinoic acid) and several synthetic compounds known as retinoids.[39] Results of previous studies[40-42] indicate a protective effect for retinoids in chemical-induced neoplasias of the bladder in rats and mice. Mechanisms of the anticarcinogenic action of retinoids have been hypothesized to include control of cell differentiation and clonal expansion of initiated cells.[39] Carotenoids are lipid-soluble substances that may alter membrane structure or integrity, making the cell or nuclear membrane impenetrable to the carcinogen. They may also act as antioxidants, disable the carcinogenic potential of certain chemicals, and suppress the proliferation of early preneoplastic lesions.[34] β-Carotene and α-carotene, including lutein, inhibit tumor development in the lung, skin, liver, and bladder of rodents.[43,44]

Similar to findings in most epidemiologic studies in humans, our study detected no distinctions between consumption of raw or cooked vegetables. Cooking did not appear to negate the benefits of consuming green vegetables in a study[15] of bladder cancer (92% cases of TCC) among Seventh-day Adventists in the United States. In that study, the risk of bladder cancer was decreased by 60% for those consuming cooked green vegetables at least once per day.

The anticancer activity of cruciferous vegetables is thought to result from the activity of isothiocyanates, which are derived from glucosinolates.[45,46] Isothiocyanates suppress activation of carcinogens and enhance detoxification of carcinogens by increasing the activities of detoxifying enzymes that convert harmful substances into less harmful hydrophilic metabolites that can readily be excreted from the body.[45,46] Epidemiologic studies in humans suggest that consumption of cruciferous vegetables either ≥ 3 times/wk or in ≥ 5 servings/wk is associated with a 25% or 50% reduction, respectively, in the risk of developing urinary bladder cancer.[12,19]

Previous studies[27,28] in humans have revealed a reduction in the risk of developing bladder cancer in association with long-term use of daily multivitamin and vitamin E supplements and a dose-response relationship for the duration of vitamin E supplementation. Supplementation of vitamin C reduced the risk of developing bladder cancer by > 40% among elderly humans.[24] Vitamins C and E are potent antioxidants that may inhibit carcinogenesis by neutralizing reactive oxygen species, inhibiting the formation of potential carcinogens such as nitrosamines, or enhancing immune function.[39]

In the present study, the decreased risk of developing TCC in dogs consuming cruciferous vegetables at

least 3 times/wk or receiving daily supplementation with vitamins C and E was not significant. The lack of significance may have been a result of inadequate sample size. Even among the control dogs, the proportion of dogs fed cruciferous vegetables or given vitamin supplements was ≤ 10%. This low prevalence in a study population of 175 yielded a 60% power to detect an 80% decreased risk of TCC associated with consumption of cruciferous vegetables.[30] The power to detect a protective effect of vitamins C and E was also low (25%).

The daily diet for dogs in this study was relatively homogenous: > 50% of the study dogs consumed a diet that consisted predominantly (≥ 90% by volume) of commercial dry dog food for a mean of 8 years. Dogs were fed vegetables in addition to this basic diet. Thus, a major strength of our study may have been the minimal variability and long-term consistency in the basic diet of the study animals. However, as is true for studies investigating the effects of diet on cancer in humans, there may be other nondietary factors associated with the feeding of vegetables that confounded results of this study. Multivariate logistic regression was used to control for host factors such as age, weight, and neuter status. However, dogs regularly fed vegetables may also have unknown characteristics associated with a reduced risk of developing TCC that were not accounted for in the analyses applied. Only randomized trials can adequately control for such unknown confounding factors and establish proof of the protective effect of regular consumption of vegetables on the risk of developing neoplasia. Without data from such trials, the importance of results of case-control studies remains speculative.

Diet information pertained specifically to the 1-year period before the diagnosis of TCC was made for case dogs, and for a comparable time period for the control dogs, to minimize errors in recall of past diet. This diet information was considered to be a surrogate for earlier dietary patterns. There was a potential for bias in the reporting of dogs' diets by participating owners. However, because owners were not aware of the hypothesis of the study, errors in reporting the dogs' diets would not have been influenced by the case or control status of the dogs.

In this report, an inverse association was detected between 3 times/wk consumption of vegetables, specifically consumption of green leafy and yellow-orange vegetables, and the risk for developing TCC in Scottish Terriers. This finding suggests that there are potential neoplasia-preventive benefits associated with consumption of certain vegetables.

a. SAS, version 8.2, SAS Institute Inc, Cary, NC.
b. Proc Logistic, SAS Institute Inc, Cary, NC.

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