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Moving Beyond Diet and Colorectal Cancer

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Colorectal Cancer (CRC) is the third in incidence and mortality from all cancers worldwide with rates paralleling economic development and a westernized lifestyle (1, 2). The majority of CRC cases occur sporadically, with environmental influences such as diet, exercise, alcohol, and smoking viewed as risk factors. In addition, CRC is associated with increasing age, as the majority of CRC cases are diagnosed in individuals who are 60 years or older.

CRC develops from pre-cancerous lesions (adenomas or polyps) to malignant adenocarcinoma through genetic mutations altering the cell growth cycle (3). It is believed that it takes 10–15 years for an adenoma to develop into an adenocarcinoma, thus, highlighting the importance of exposure and time for environmental factors. A recent review by the World Cancer Research Fund/American Institute for Cancer Research states that while there is convincing evidence that reduced physical activity, increased abdominal adiposity, increased red meat and processed meat intakes elevate CRC risk, there is limited evidence to suggest the protective effects of fruits and non-starch vegetables for CRC risk (4). Since tumor location (left vs right-sided cancers) centers on the potential different biological pathways that may be responsible for carcinogenesis (5), studying fruit and vegetable intake based on cancer sub-sites remains to be explored.

Current Research

In this issue of the *Journal*, Annema et al. present a population based case-control analysis (824 cases and 939 controls) of the association between fruit and vegetable consumption and risk of Colorectal Cancer (CRC) by subsites of the large bowel (proximal colon, distal colon, rectum), from the Western Australian Bowel Health Study. Participants were first incident cases diagnosed during the study period and enrolled in the Western Australia Cancer Registry; controls were obtained via electoral rolls. Data was collected through self completed postal questionnaires; diet intake was assessed by a 74-item food frequency questionnaire (FFQ) developed by the Cancer Council Victoria aimed at assessing dietary intake ten years earlier. Total and subgroups for fruit and vegetable intakes were quantified

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as daily equivalent frequencies and divided into quartiles. BMI was calculated from self-reported height and weight at age 20. Individuals were categorized on diabetes and smoking status, physical activity level, and socio-economic index. Cases and controls were frequency matched on age and sex. Odds ratios and a test of trends were calculated across quartiles of fruit and vegetable intakes, adjusting for covariates. In addition, analyses for all CRC cases were performed by tumor site.

Differences between cases and controls were found. Proximal cases of colon cancer were older and more likely to be female while cases of rectal cancers were more likely to be males compared to controls. Controls were also more likely underweight (at age 20) compared to all case (tumor site) groups. Participants with distal and rectal cancers drank more than 30g of alcohol a day than controls. Cases also lived in lower socioeconomic regions than controls.

Multivariate modeling for overall CRC risk demonstrated no association between total fruit and vegetable intake (together and separate), however when subgroups were analyzed, intake of apples (highest to lowest quartile) and dark yellow vegetables (second, third quartiles compared to lowest) were significantly associated with a decreased CRC risk. In contrast, intake of fruit juice (highest to lowest quartile) was associated with an increased risk of CRC with significance for a trend.

When multinomial modeling was performed to examine the risks by cancer site, the results appeared similar to the overall CRC risk. Intake of fruits and vegetables was not associated with proximal colon cancer and rectal cancer risk. In addition, similar to the overall CRC models, intake of dark yellow vegetables (Q4 vs Q1, OR= 0.61 95% CI: 0.41–0.92) and apples (Q4 vs Q1, OR= 0.51 95% CI: 0.34–0.77) were significant for a protective effect for distal colon cancers and fruit juice (Q4 vs Q1, OR= 1.74 95% CI: 1.24–2.45) was associated with an increased risk for rectal cancers. The exceptions in cancer site risks compared to overall CRC risk were that distal colon cancers exhibited a significance for a protective effect (Q4 vs Q1, OR= 0.58 95% CI: 0.36–0.93) for total fruit and vegetable intakes and intake of brassica vegetables were protective for proximal colon cancer risk (Q4 vs Q1, OR= 0.62 95% CI: 0.41–0.93).

These findings are similar to previous findings in meta-analyses where weak or no associations were reported (4); however, the analysis by cancer site provides new information. Historically nutritional epidemiology has relied on using the dietary intake model to assess cancer risk without accounting for other factors involved in the carcinogenesis pathway and frequently relying on self report for anthropometric data. Information on obesity related exposures like insulin resistance, inflammation, aspirin as well as their genetic predisposition modifies CRC risk. Failing to simultaneously evaluate these components and reliance on self report for obesity and other conditions that influence CRC risk in studies assessing the impact of dietary intake likely explains many of the negative and variable findings. The influence of these exposures is briefly reviewed below.

Insulin resistance

Insulin resistance (IR) marked by high circulating levels of insulin has been shown to increase risk of CRC by almost 40% (6, 7). Markers for insulin secretion (e.g. serum-C peptide) require a blood sample and were beyond the scope of the investigation. Instead Annema et al. relied on self report measures for diabetes status and did not find differences between CRC (all and subsites) and controls. Data on history of pre-diabetes or insulin resistance (i.e. metabolic syndrome) was not explored. The manifestation of diabetes is often initiated through elevated insulin or hyperinsulinemia. The model used to explain the role of IR and increased CRC risk has relied on levels of insulin and insulin-like growth factor in

circulation(8), with the idea that insulin may act to enhance tumor growth and reduce apoptosis in the colonic tissue (9). According to the NIH, of the 25.8 million individuals with diabetes, over 27% (7 million) are unaware of their condition (10); the lack of association between groups may be at least partially due to how diabetes was classified.

Obesity and inflammation

Annema et al used a self reported BMI at age 20 to characterize the adiposity of the participants in the study. While correlations between self-report and actual measured weight are high (i.e. r 's > 0.90) (11), when errors occur they tend to be in the direction of underreporting weight and overreporting height (12). Systematic biases are also likely. For example, women are more likely to underreport weight than men, as are individuals who are attempting to lose weight and those with higher BMI's (13). Because cases are more likely to be obese their reliance of self-report likely somewhat diminished their ability to detect the influence of these variables on CRC risk. Several large prospective cohort studies have consistently demonstrated positive associations between obesity and colorectal cancer with a dose-response for risks between BMI and waist circumference (14).

As stated earlier, the progression of healthy colonic mucosa to adenocarcinoma takes several years. Obtaining the participants BMI at CRC diagnosis and at age 20 would have provided more complete information on their adiposity exposure. Americans and Europeans gain 1–2 lbs annually (15, 16) and this pattern of weight gain in Australians is likely similar to those observed in other westernized nations. Additionally, a question discerning if they had experienced a greater than 3% weight change in the past year would have allowed detection of sudden weight loss which is a symptom of CRC.

Obesity is characterized by a chronic low-grade inflammatory state with elevations in circulating cytokines and other inflammatory mediators (17). A recent study found that the colonic mucosa of obese individuals are inflamed with elevations in pro-inflammatory cytokines (IL-6, TNF- α) and transcription factors (STAT3, NF- κ B), and following low calorie induced weight loss improved these markers (18). Accounting for the inflammation effect is critical since (a) inflammation status may impact CRC (colitis associated CRC heightens one's lifetime risk significantly) (b) Similar mechanisms with elevations of these mediators may also induce carcinogenesis in obesity (19). A five-unit increase in BMI or increase in waist circumference (per 10-cm) has been shown to increase the risk of CRC by about 15% in women and 30% in men (14).

NSAID Use

One of the limitations in the analysis by Annema et al is their lack of data on medication use, specifically the use of Non-Steroidal anti-inflammatory (NSAID) drugs (e.g. aspirin, ibuprofen). NSAIDS inhibit cyclooxygenase (COX-1 and COX-2), involved in the production of prostaglandins, thus creating an anti-inflammatory effect (20). Since inflammation plays a role in CRC, the recommendation of NSAID use in CRC prevention has been extensively studied over the years. Large prospective cohorts such as the Nurses' Health Study (21) and Health Professionals Follow-up Study (22) have demonstrated the protective benefits of regular aspirin use and reduced adenoma and CRC risk. In addition, a recent meta-analysis of randomized clinical trials reported low-dose aspirin (i.e. baby aspirin) use over 20 years significantly reduced CRC incidence by about 30% (23).

Brassica vegetables and genetic polymorphisms

Since plant diet contains bioactive phytochemicals, the idea of how genetic variation may be a factor to modify the body's response with handling these compounds should be discussed

with CRC risk. Understanding how interindividual differences may exist with plant based diets may explain the complexity for implications in cancer risk (24). One of the subgroups of vegetable intake that demonstrated a protective effect in this study was with brassica vegetables. Brassica vegetables include cabbage, sprouts, broccoli and cauliflower. One of their active secondary metabolites, glucosinolates, may exhibit anti-carcinogenic effects. These vegetables were found to be associated with lower risks in proximal colon cancer risk however this may have been attributable to the status of genetic polymorphisms of glutathione-S-transferase (GST) enzymes in these individuals. Lin et al. (25) conducted a case control study of the risk of colorectal adenomas in patients who were null for GSTM1 and found those in the highest quartile of broccoli intake had approximately a 50% reduction in adenoma risk compared to those in the lowest quartile. They speculated this was due to slower breakdown of the glucosinolate products which contributed to a 'detoxification system' (25, 26). In contrast, Tijhuis et al (27) demonstrated that individuals with a single nucleotide polymorphism in GSTP1, there was about a 90% increased risk for adenomas for the highest consumers of brassica vegetables. While the effect of gene alterations on one family of enzymes may constitute a fraction of differences, these discrepant findings illustrate the complexity of studying diet and CRC. Almost half of the human population cannot express important GST activity due to genetic predisposition, therefore further understanding on the intake of brassica and protective effects for CRC will require monitoring these genes which can impact the detoxifying effects in the colon.

Summary

The study by Annema and colleagues provides new findings in the role of fruit and vegetable consumptions and risk of colorectal cancer by subsites, though overall assessment of diet and colorectal risk needs to be reexamined. The inability to see a clear protective effect of fruit and vegetable consumption agrees with the literature and the World Cancer Research Fund/American Institute for Cancer Research (4). Using a case control study design and self report for exposure introduces error as data is collected after disease diagnosis. Also, the null associations observed in the fruit and vegetable intake and cancer literature needs to be expanded to address the complexity of other environmental influences that impact the impact of their exposure. The assessment of dietary via their validated FFQ was optimal, however the exclusion of other known nutrition-related influences such as history of weight gain and insulin resistance may have limited their ability to detect differences between cases and controls. Clinicians and researchers need to understand the broader issues in CRC risk, including indicators of inflammation, medication use, and genetic predisposition in future large cohort studies.

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