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Phytoestrogens and colorectal cancer prognosis

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There is evidence from experimental and human studies that endogenous hormone exposure and hormone replacement therapy play a role in carcinogenesis and progression of colorectal cancer. The evidence is limited and inconsistent with respect to the dietary phytoestrogens, an estrogenic compound derived from plants. Phytoestrogens have a similar structure to endogenous estrogen which enables them to bind estrogen receptors and activate pathways related to anti-carcinogenic and anti-progression actions.

First, a literature review and meta-analysis was conducted to synthesize the current knowledge on the association between phytoestrogens and colorectal cancer risk, since only one study was available on colorectal cancer prognosis. In general, overall phytoestrogen exposure was associated with colorectal cancer risk, while the significant association was only observed in case-control studies but not in cohort studies. The results also differed by phytoestrogen subgroups and phytoestrogen assessment method. The observed heterogeneity precluded a rigorous conclusion on the association of overall phytoestrogens and colorectal cancer risk. The results indicated the importance of an accurate assessment method and separate analyses by phytoestrogen subgroups in the following analyses on colorectal cancer prognosis. Potential differential association according to participant and tumor characteristics has scarcely been studied and should also be considered.

A German population-based prospective patient cohort of stage I to stage III colorectal cancer derived from Darmkrebs: Chancen der Verhütung durch Screening study was used to assess the association between phytoestrogen and colorectal cancer prognosis. The concentration of phytoestrogens was quantified in serum using ultra-performance liquid chromatography/ mass spectrometry. Potential effect modification of the associations between phytoestrogens and colorectal cancer prognosis was assessed according to patient characteristics, tumoral characteristics and molecular characterization, treatment, and timing of blood draw.

Of six phytoestrogen subgroups measured, only 2 subgroups (genistein and luteolin) could be detected in the majority of the patients and therefore used for the subsequent analyses. Late-entry Cox regression models were used to estimate the hazard ratios and 95% confidence interval after adjusting for relevant confounders from the backward selection. Effect modifiers were assessed using the likelihood ratio test. Restricted cubic spline models were used to assess potential a

non-linear dose-response relationship between phytoestrogens and prognosis of colorectal cancer, separately for genistein and luteolin.

Of 2072 stage I- III colorectal cancer patients, genistein and luteolin were detected in 2051 and 2037 patients, respectively. The median (interquartile range) of serum genistein and luteolin was 12.31 ng/μL (10.48-14.50) and 7.39 ng/μL (6.58-8.34), respectively. During a median of 5.2 years of follow-up after diagnosis, 486 deaths, 256 colorectal cancer-specific deaths, 403 colorectal cancer recurrences, and 313 distal metastasis events were documented. Compared with the lowest quartile, the highest quartile of serum genistein concentration was not significantly associated with colorectal cancer prognosis. The hazard ratios (95% confidence interval) for overall mortality, colorectal cancer-specific mortality, colorectal cancer recurrence, distal metastasis and disease-free survival were 1.06 (0.82-1.36), 0.88 (0.62-1.26), 0.98 (0.72-1.33), 0.88 (0.62-1.25) and 1.04 (0.81-1.33), respectively. Similar associations were observed for serum luteolin and the corresponding hazard ratios (95% confidence interval) were 1.14 (0.89 - 1.46), 0.96 (0.69 - 1.34), 0.99 (0.74 - 1.32), 0.93 (0.67 - 1.29) and 1.12, (0.89 - 1.42). However, the association might be differential by chemotherapy. Compared with the lowest quartile, hazard ratios (95% confidence interval) of the highest quartile of serum genistein for overall mortality in those with and without chemotherapy were 0.74 (0.48-1.14) and 1.51 (1.03-2.23) (P-interaction=0.02). For luteolin, hazard ratios (95% confidence interval) for CRC recurrence in patients with and without chemotherapy were 0.63 (0.42-0.96) and 1.53 (0.97-2.40) (P-interaction: 0.03), while the corresponding hazard ratios (95% confidence interval) for disease-free survival were 0.74 (0.51-1.08) and 1.43 (1.00-2.04) (P-interaction: 0.02), respectively. No differential effect by the expression of estrogen receptor beta was observed for both genistein and luteolin.

To explore modulation of deoxyribonucleic acid methylation as a potential mechanism through which phytoestrogen may influence clinical outcomes among colorectal cancer patients, an epigenome-scan was conducted on genistein and luteolin concentration in a subset of patients (discovery set). Replication of the significant cytosine-phosphate-guanine sites was attempted in an independent subset (replication set). The discovery set included 903 colorectal cancer patients for genistein and 884 patients for luteolin analysis, while the replication set included 750 for genistein and 752 for luteolin. Two cytosine-phosphate-guanine sites (chromosome 1:cg22684507 and chromosome 8: cg04219515) were found associated with luteolin concentration in the discovery set. However, none of them could be confirmed in the replication set.

In conclusion, the present study provides limited evidence that serum genistein or luteolin could influence the colorectal cancer prognosis. However, significant effect heterogeneity by chemotherapy was observed. Genistein and luteolin may be associated with a better prognosis among patients receiving chemotherapy and a poorer prognosis among those without. Larger studies are warranted to confirm the finding of interaction with chemotherapy and to elucidate the potential mechanisms involved.