Inflammatory Biomarkers May Signal Higher Risk of Esophageal Adenocarcinoma

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Esophageal adenocarcinoma is a rare, but increasingly common, cancer. Since many cases of are diagnosed at later stages of disease, the mortality rate is high. Individuals with Barrett's esophagus are at substantially higher risk of esophageal adenocarcinoma, though the absolute risk of progression is low. Identifying individuals at increased risk of progressing from Barrett's esophagus to esophageal adenocarcinoma could greatly improve outcomes through earlier detection. Inflammatory biomarkers have been used to help predict onset of other cancers, but have not previously been assessed for esophageal adenocarcinoma. In a recent report in *Cancer Epidemiology, Biomarkers & Prevention*, Drs. Sheetal Hardikar, Thomas Vaughan, and colleagues in the Public Health Sciences Division found that higher levels of the inflammatory biomarkers C-reactive protein and interleukin-6 are associated with an increased risk of progression from Barrett's esophagus to esophageal adenocarcinoma.

There are several ways through which inflammation might contribute to cancer development, such as through DNA damage, inhibition of apoptosis, angiogenesis, or promotion of cellular proliferation. Importantly, while cancer-promoting processes might take place at a localized spot, they lead to systemic inflammatory responses that can be easily assessed in the blood through representative biomarkers such as C-reactive protein and interleukin-6. As several chronic inflammatory conditions in the gastrointestinal tract have previously been associated with cancer, these inflammatory biomarkers hold promise as a potential biomarker of progression from Barrett's esophagus to esophageal adenocarcinoma.

To evaluate this relationship, the authors utilized samples and data from the Seattle Barrett's Esophagus Study (SBES). This well-characterized prospective cohort study includes serial assessments of participants with Barrett's esophagus for up to 17 years of follow-up. Blood samples from baseline and later were measured for mean C-reactive protein and interleukin-6 levels, and individuals who progressed were compared to those who did not. After adjustment, the authors found that mean C-reactive protein levels above the median were associated with an 80% increased risk of esophageal adenocarcinoma compared to those with mean values below the

median. Similarly, mean interleukin-6 levels above the median also demonstrated a nearly two-fold increase in risk compared to those with mean values below the median.

These results, said lead author Dr. Hardikar, "suggest that minimally-invasive measurements of circulating markers of inflammation, particularly C-reactive protein and interleukin-6, may help identify persons at higher risk of progression to cancer from those who are likely to follow a benign course." Being able to stratify patients into different levels of risk would be beneficial, as "surveillance and prevention efforts could potentially be targeted to the subset of patients with the highest risk, substantially reducing cost, patient anxiety, and potential morbidity" (see figure). Additionally, these inflammation markers have the potential to provide a less-invasive alternative to current surveillance methods, which involve periodic endoscopic examinations. If validated, this could enhance surveillance compliance and reduce the number of endoscopy-related complications.

While these results are encouraging, said Hardikar, "further research is needed to evaluate the role of inflammation in esophageal adenocarcinoma development among those with Barrett's esophagus. Currently, we are evaluating these markers as part of a panel of demographic, lifestyle and other biomarker predictors to develop a population risk model for esophageal adenocarcinoma, which may lead to significant improvement in clinical management of Barrett's esophagus."

Other PHS investigators contributing to this project were Drs. Lynn Onstad, Xiaoling Song, Mario Kratz, Garnet Anderson, Patricia Blount, Brian Reid, and Emily White.

Hardikar S, Onstad L, Song X, Wilson AM, Montine TJ, Kratz M, Anderson GL, Blount PL, Reid BJ, White E, Vaughan TL. 2014. Inflammation and oxidative stress markers and esophageal adenocarcinoma incidence in a Barrett's esophagus cohort. *Cancer Epidemiol Biomarkers Prev*. pii: cebp.0384.2014. [Epub ahead of print]

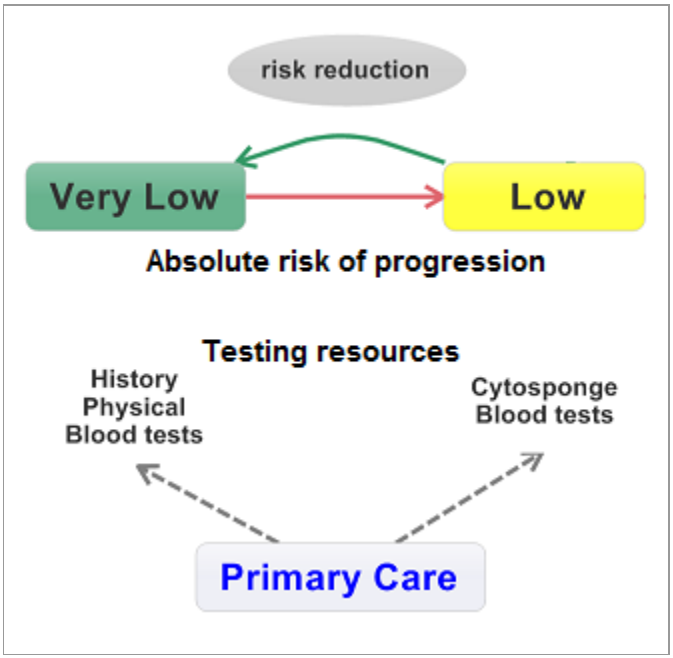

Image provided by Dr. Sheetal Hardikar.

Within the primary care setting, blood tests for inflammatory biomarkers such as C-reactive protein and interleukin-6 could be utilized to identify patients with Barrett's esophagus whose absolute risk of progression has increased. Risk reduction strategies could then be utilized in this group to lower their risk.