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Do sex hormones underlie sex differences in cancer incidence? Testing the intuitive in esophageal adenocarcinoma.

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Abstract

Esophageal adenocarcinoma (EA) incidence is 4–8 times higher in men compared with women, yet this imbalance cannot be explained by known risk factors. This issue of the American Journal of Gastroenterology features results from only the second prospective study to assess whether prediagnostic sex steroid hormones underlie sex differences in EA. Xie and colleagues report that higher concentrations of testosterone and luteinizing hormone were associated with decreased EA risk. While contrary to the long-standing hypothesis that testosterone increases EA risk, these important results lay a foundation for additional studies to further elucidate this intuitive, intriguing, and evolving hypothesis.

Editorial

In Western countries, esophageal adenocarcinoma (EA) incidence increased approximately 300–600% between the 1970's and early 2000's, but rates have stabilized in recent years (1, 2). A constant, enigmatic observation of EA throughout this period has been the 4–8 times higher incidence in men compared with women (3). Known risk factors for EA that differ in prevalence by sex, such as obesity, reflux, and smoking, explain very little of the skewed sex ratio (4, 5). In 1998, Lagergren and Nyrén first hypothesized that sex steroid hormones may account for sex differences in EA (6). Although a seemingly intuitive hypothesis, sex steroid hormones—the primary drivers of the development and homeostasis of secondary sexual characteristics—are known to have carcinogenesis-related roles including cellular proliferation and differentiation, metabolism, inflammation, and apoptosis. In addition, other studies have reported estrogen receptor expression in EA tissue (7-9); lower rates of EA among men with prostate cancer, who are likely receiving anti-androgen therapies (10-13); and, in women, reproductive factors and hormone replacement therapy associated with lower EA risk (14, 15).

Fast-forward twenty years from Lagergren and Nyrén's hypothesis, the maturation of large, prospective cohort studies made it possible for our group to publish the first study of prediagnostic sex steroid hormones in relation to EA risk (16). In that study, we assessed both EA and gastric cardia adenocarcinoma (GCA) as a combined outcome, drawing 259

male cases and 259 matched male controls from across three parent cohort studies. We found that higher concentrations of dehydroepiandrosterone (DHEA) and estradiol were associated with decreased EA/GCA risk, but we did not find a significant association with testosterone.

In this issue of the *American Journal of Gastroenterology*, Xie *et al.* report the results from only the second prospective study on this topic, examining prediagnostic circulating sex steroid hormones in 244 male EA cases and 244 matched male controls (17). Their study has the advantages of focusing solely on EA as well as accrual of cases and matched controls from a single country (Norway) (18, 19), alleviating concerns of etiologic heterogeneity by anatomic location (20) and geography (3), respectively. In this study, the authors report that higher concentrations of testosterone and luteinizing hormone (LH) were associated with decreased EA risk (17).

Xie *et al.* then meta-analytically combined their study results with our prior results for each of the five overlapping hormone metrics—testosterone, estradiol, testosterone:estradiol ratio, androstenedione, and sex hormone-binding globulin. In the meta-analysis of testosterone—measured in both studies using mass spectrometry—they found higher concentrations of testosterone to be associated with a significant 40% reduced EA/GCA risk (17), which does not appear to be explained solely by body mass index (16, 17). This result is also in-line with the findings of a prior case-control study we conducted (21), albeit with the greater likelihood of reverse-causation. Although the inverse testosterone-EA association is contrary to the original hypothesis that testosterone increases risk (6), these observations may lead to novel hypotheses explaining the enigmatic sex differences. For example, obesity is the strongest known risk factor for EA (22) and is associated with metabolic endotoxemia, defined as small increases of circulating lipopolysaccharide (23). Metabolic endotoxemia is associated with proinflammatory cytokines, including sTNFR2 (24), which was identified as a potential mediator of the obesity-EA association (25). Further, lipopolysaccharide may influence EA risk by relaxing the lower esophageal sphincter and delaying gastric emptying (26). Additionally, endotoxin-initiated inflammation reduces testosterone levels, even among healthy, lean men (27). Thus, the testosterone-EA association could be a downstream effect of an alternative mechanism, such as metabolic endotoxemia.

The meta-analysis of estradiol did not replicate our prior reported inverse association with EA (16). However, there are notable differences in both the laboratory and statistical methods between the two studies. Xie *et al.* used immunoassays to measure the majority of hormones, including estradiol (17). Immunoassays have low analytic sensitivity (28), as evidenced by 36% of the estradiol measurements being below the lower limit of detection (LLOD) which led to analytic categorization into three groups—below LLOD and dichotomization of the remaining quantitated samples. The resultant misclassification and partial ascertainment of estradiol variability provides for an imperfect comparison to our prior study, which assessed quartiles of estradiol exposure derived from mass spectrometry with less than 1% of the samples below the LLOD (16). This highlights the necessity of using mass spectrometry to accurately quantitate estradiol in men (29) and leaves open the possibility that estradiol shares an association with EA risk.

Another notable difference between the two studies is the metabolites targeted, specifically LH and DHEA. In the current study, Xie *et al.* reported that higher levels of LH was associated with a 45% decreased EA risk (17), but we did not previously measure any of the gonadotropins (16). Further, the current study measured sulfated DHEA (DHEA-S), which cannot bind to estrogen receptors and is a poor correlate of the active metabolite DHEA (30), which we previously found to be associated with a 72% decreased EA risk (16). In addition to testosterone and estradiol, the associations of LH and DHEA with EA clearly merit further follow-up.

In sum, this study underscores the difficulty of explaining a simple observation in EA incidence—constant, enigmatic higher rates in men compared with women. Further research is necessary to elucidate the putative inverse associations of testosterone, estradiol, LH, and DHEA with risk of EA. Primary challenges will be achieving sufficient statistical power—particularly for assessing these exposures in women, given the lower incidence of EA—and attaining a sufficient volume of prediagnostic serum/plasma to conduct a broad study of sex hormones using mass spectrometry-based technologies. To achieve these goals, an international consortium study will be required. Additionally, complementary studies that quantitatively capture the spatial distribution of steroid hormone receptors in esophageal tissues across the disease continuum are needed. The combination of circulating and tissue-based studies would build on the important observations of Xie *et al.*, further elucidating what is an intuitive, intriguing, and evolving hypothesis.

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