Editorial

Seeing red: diet and endometriosis risk

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Endometriosis is an estrogen-dependent chronic gynecologic disorder that significantly reduces the quality of life of affected women. Characterized by adhesions of endometrial fragments in extra-uterine sites (predominantly in the peritoneal cavity and ovary but occasionally on the diaphragm, liver, and abdominal wall), the condition occurs in ~10% of the general population and is associated with infertility, pelvic pain, and increased risks for ovarian and other cancers (1,2). Our understanding of its etiology and complex, multi-factorial origins remains inadequate (3-5). Moreover, its asymptomatic nature at the early stages can significantly delay clinical diagnosis. Treatment options are currently limited to hormonal therapy or surgical management; however, these methods are non-curative, may not align with women's reproductive goals, and frequently lead to recurrence after cessation of treatment (6). Delineating the factors that contribute to lesion development and progression is key to providing opportunities for prevention and more efficacious therapeutic interventions.

Diet is a leading risk factor for many chronic diseases (7,8). The linkage between diet and endometriosis, summarized in a recent review (9), underscores the ability of anti-inflammatory components present in foods to mitigate endometriosis. Nevertheless, there are certain caveats to consider. Notably, most reported studies which support the linkage were conducted using animal models of endometriosis and findings were simply extrapolated to humans. Moreover, in the few studies with affected women, the investigations were predominantly retrospective or case-control, which are prone to selection and/or recall bias and were typically too limited in duration to sufficiently illuminate effects of dietary interventions on lesion development and progression. In the recent paper by Yamamoto *et al.* (10), the authors report on a prospective cohort study that evaluated the association between intake of red meat, poultry, fish and seafood on the risk of laparoscopically-confirmed endometriosis. In this work, the authors provide important insights on a role for diet in the development and progression of human endometriosis, and highlight important areas for future research. This manuscript is notable for several strengths in study design. First, a large number of pre-menopausal women (total of 81,908 from The Nurses' Health Study II) with intact uteri and with no prior diagnosis of endometriosis or cancer (except for skin melanoma in a few cases) were followed for a duration of over 20 years (1991 to 2013). Second, diet was assessed using an extensively validated semi-quantitative food frequency questionnaire that incorporated portion size and frequency of intake. Third, endometriosis was laparoscopically-confirmed, obviating uncertainties in diagnosis. The 3,800 cases (women), representing 1,019,294 person-years of follow-up, provided a strong platform to advocate significant dietary influences on endometriosis risk.

From this important data set, we learn that intake of red meat, either as processed or unprocessed, is a major culprit in promoting endometriosis risk (hence, seeing red). Replacement of red meat with fish, shellfish or eggs

was associated with lower risk of endometriosis. A quite unexpected result was the rise in endometriosis risk with increasing intake of poultry, albeit this was not as robust as seen for red meat. Yet another surprising finding is that the effect of red meat is independent of animal fat or its most common saturated fatty acid, palmitic acid. The take-home message of the study is consistent with that of a recent report that fish intake relative to red meat, lowers the risk of type 2 diabetes, yet another chronic disease (11). Interestingly, with type 2 diabetes, poultry consumption showed protective effects not noted with endometriosis.

This research sheds light on potential nutrients that may promote red meat's observed effects on endometriosis risk. The intriguing possibility that heme iron constitutes a major component responsible for the negative effects of red meat consumption is consistent with a previous report suggesting a potential association between heme, which is abundant in red meat, and colon cancer risk (12). In that study, colonic epithelia of rats fed heme-supplemented diet showed higher proliferation rates when compared to those of control counterparts, irrespective of dietary fat content. In a population case-control study of adenocarcinoma of the esophagus and stomach, Ward *et al.* (13) reported that higher intake of heme iron and total iron from meat sources constitutes a risk for these cancer types. Iron can cause oxidative stress and DNA damage and heme iron catalyzes the endogenous formation of *N*-nitroso compounds, which are potent carcinogens (13). However, the heme iron hypothesis in colorectal cancer posits local mutagenic effects, which may not be easily extrapolated to ectopic lesion development.

A number of important points are worth considering from Yamamoto *et al.*'s study. First, the significant increase in endometriosis risk associated with red meat was found from comparing women consuming ≥2 servings per day (equivalent to 14 servings or more per week) with women consuming ≤1 serving per week; the latter effectively being non-red meat eaters. Interestingly, even 2–4 servings per week elicited a modest increase in endometriosis risk, suggesting that limiting red meat consumption to less than once weekly is best. Second, the study indicated that women with the highest red meat consumption (and hence, greater risk for endometriosis) were more likely to be overweight or obese and had greater caloric intake. These observations beg the question of whether the frequency of eating red meat contributes to higher body mass index (BMI) and are seemingly inconsistent with previous studies indicating lower BMI as a risk factor for endometriosis and a predictive factor for severe endometriosis (14,15). In a recent report (16), mice experimentally-induced with endometriosis exhibited lower body weights than sham controls (non-endometriotic mice) with *ad libitum* feeding. The study's authors posited that endometriosis may be causal to rather than a consequence of, loss of body weight and body fat due to the accompanying disruption of hepatic metabolic gene expression (16). In a related study using another mouse model of endometriosis (17), high fat-diet promotion of endometriosis occurred in the absence of weight gain, ovarian dysfunction and insulin resistance, but was associated with increased systemic inflammation and oxidative stress. Since metabolic dysfunction rather than BMI is more highly correlated with many chronic diseases (18), the latter commonly characterized by persistent low levels of inflammation, the analyses of pro-inflammatory cytokines and metabolites from Yamamoto *et al.*'s patient cohort may help address the lingering question on the association between diet, endometriosis and metabolic status. Third, given the estrogen-dependent nature of endometriosis, the authors raise the likelihood that red meat may increase endogenous levels of estrogen in substantial red meat consumers. This is an arguable point since serum levels of estradiol in women with and without endometriosis are comparable (19), although the possibility that local (endometrial tissue) estrogen synthesis is elevated with increased red meat intake cannot be excluded. Harmon *et al.* (20) compared the levels of estrogens (estrone and estradiol) in sera of premenopausal women with low (considered semi-vegetarians) and high meat (red meat, poultry) intake, and found that serum estrogens were lower in semi-vegetarians than non-vegetarians. However, that study was limited by small sample size, and further data are required to clarify this association. Finally, with the mounting evidence that a woman's exposure to environmental disrupting chemicals can modulate her reproductive system beginning at early life (21), it is possible that organic pollutants present in farmed animal products may contribute to increased risk of endometriosis. While fish and shellfish are similarly subject to environmental insults, the specific contaminants and the degree of contamination may be different between the animal groups.

Distinct dietary protein sources (e.g., red meat, poultry, fish, eggs), which are known to differ by amino acid composition and fatty acid content were compared in Yamamoto *et al.*'s report. In recent years, the potential link between dietary protein source and the composition of the

gut microbiota has gained considerable ground (22,23). The participation of the gut microbiota in the pathogenesis of endometriosis has been posited as well, based on the role of the gut in regulating signaling molecules that orchestrate inflammatory, immune and proliferative pathways (24). Coming from another viewpoint, Yuan *et al.* (25) demonstrated significant changes in gut microbiota composition during the development of endometriosis in a mouse model. While the validity of a potential bidirectional relationship between endometriosis and the microbiota has yet to be confirmed in humans, the notion that dietary-induced changes in the intestinal milieu can influence endometriosis and vice-versa, may lead to a more personalized approach and novel biomarkers to reduce the risk for this condition.

The study by Yamamoto *et al.* lays the foundation to better understand how the multi-faceted nature of endometriosis may be managed by simple dietary changes and provides a compelling case for women of reproductive-age to reevaluate their dietary habits for the prevention of chronic disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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