GYNECOLOGY

# A prospective cohort study of meat and fish consumption and endometriosis risk

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**BACKGROUND:** Only 2 case-control studies have examined the associations between consumption of meat products and endometriosis risk with inconsistent results. Consumption of animal products has the potential to influence endometriosis risk through effects on steroid hormones levels.

**OBJECTIVE:** We sought to determine whether higher intake of red meat, poultry, fish, and seafood are associated with risk of laparoscopically confirmed endometriosis.

**STUDY DESIGN:** A total of 81,908 participants of the prospective Nurses' Health Study II were followed up from 1991 through 2013. Diet was assessed via food frequency questionnaire every 4 years. Cox proportional hazards models were used to calculate rate ratios and 95% confidence intervals.

**RESULTS:** During 1,019,294 person-years of follow-up, 3800 cases of incident laparoscopically confirmed endometriosis were reported. Women consuming >2 servings/d of red meat had a 56% higher risk of endometriosis (95% confidence interval, 1.22—1.99; $P_{trend} < .0001$) compared to those consuming ≤1 serving/wk. This association was strongest for nonprocessed red meats (rate ratio, 1.57; 95% confidence interval, 1.35—1.83 for ≥2 servings/d vs ≤1 servings/wk; $P_{trend} < .0001$), particularly among women who had not reported infertility ($P_{interaction} = .0004$). Women in the highest category of processed red meat intake also had a higher risk of endometriosis (rate ratio, 1.20; 95% confidence interval, 1.06—1.37 for ≥5 servings/wk vs <1 serving/mo; $P_{trend} = .02$). Intakes of poultry, fish, shellfish, and eggs were unrelated to endometriosis risk.

**CONCLUSION:** Our prospective analysis among premenopausal US nurses suggests that red meat consumption may be an important modifiable risk factor for endometriosis, particularly among women with endometriosis who had not reported infertility and thus were more likely to present with pain symptoms. Well-designed dietary intervention studies among women with endometriosis could help confirm this observation.

**Key words:** diet, endometriosis, meat

## Introduction

Endometriosis is a benign, estrogen-dependent, gynecologic condition with a prevalence of ~10% in women of reproductive age.[1] It is characterized by the presence of endometrial tissue outside of the uterus, causing inflammation and leading to the formation of scars and adhesions. Endometriosis patients experience a variety of symptoms including chronic pelvic pain and infertility. Despite that it is the third leading cause of gynecologic hospitalizations in the United States, its etiology is not fully understood.[2]

There has been an increased interest in the identification of modifiable risk factors for endometriosis, such as diet and exercise. Diet may influence endometriosis risk through its influence on steroidal hormones. For example, red meat has been shown to decrease sex hormone—binding globulin (SHBG) and increase estradiol concentrations,[3] while fish oil has been associated with lower circulating levels of series 2 prostaglandins and decreased inflammatory symptoms,[4] as well as a decrease in dysmenorrhea.[5] Estrogen up-regulates prostaglandin synthesis and evidence of positive feedback for local estrogen and prostaglandin may favor the inflammatory and proliferative characteristics of endometriosis.[6] Although there is extensive lay literature touting dietary changes to reduce endometriosis and symptoms, scientific literature in the field remains scant. An Italian case-control study reported that women with endometriosis had higher consumption of red meat and ham and lower intake of fish than women without endometriosis.[7] In contrast, a Washington state—based case-control study reported no association between intake of red meat or seafood and endometriosis diagnosis.[8]

In this prospective study, we investigated the association between intake of red meat, poultry, fish, seafood, and nutrients concentrated in red meats (iron and heme iron) and risk of laparoscopically confirmed endometriosis using data from the Nurses' Health Study II (NHSII). We also examined whether these associations differed by fertility status.

## Materials and Methods

### Study population

The NHSII prospective cohort consists of 116,429 female registered nurses who were ages 26—42 years at baseline. This cohort has been followed up from 1989 when the baseline questionnaire regarding information on disease history, demographic, anthropometric, and lifestyle risk factors was completed and subsequently, biennial questionnaires have been administered. Implied consent was assumed upon completion and return of the questionnaires. This study was approved by the Institutional Review Board of Brigham and Women's Hospital. Follow-up for this analysis included questionnaire data beginning in 1991 when 97,807 NHSII participants completed the 1991 food frequency

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## AJOG at a Glance

### Why was this study conducted?

Only 2 case-control studies have examined the associations between consumption of meat products and endometriosis risk with inconsistent results. Thus, we sought to examine the association between intake of red meat, poultry, fish, and seafood and risk of laparoscopically confirmed endometriosis in a prospective setting.

### Key findings

We observed that red meat, both processed and nonprocessed, was associated with an increased risk of laparoscopically confirmed endometriosis and this association was strongest among women who had never reported infertility.

### What does this add to what is known?

The stronger association among women who had not reported infertility suggests that the association may be due to an influence of diet on pain symptoms.

questionnaires (FFQ) and concluded in 2013. Response rates have been approximately ≥90% for each questionnaire cycle. We restricted our analyses to premenopausal women with intact uteri, with no prior diagnosis of endometriosis, or cancer (with the exception of nonmelanoma skin cancer) prior to June 1991. In addition, we excluded women with implausible total energy intake (<3347 or >17573 kJ/d), or who left >70 food items blank on the 1991 FFQ. There were 81,908 participants remaining in the study after these exclusions.

## Case ascertainment

Starting with the 1993 questionnaire, the nurses were asked if they have "ever had physician-diagnosed endometriosis." If participants reported "yes," they were asked if it was confirmed by laparoscopy, which is considered the gold standard for endometriosis diagnosis. For each subsequent questionnaire cycle, participants were asked about diagnosis of endometriosis in the preceding 2 years. From the 1766 incident cases that were identified from the initial questionnaire, a validation study was conducted the following year among 200 randomly selected cases.[9] A supplemental questionnaire was mailed to these participants requesting permission to review their clinical and surgical records. In 96.2% of the 105 cases in which laparoscopic confirmation was reported and records retrieved, endometriosis diagnosis was confirmed. Furthermore, requests to review medical records were also sent to those women who indicated having a hysterectomy during the time of endometriosis diagnosis. In 79.6% (144/188) of the records retrieved, a diagnosis of endometriosis at the time of the hysterectomy was confirmed; however, in only 5.5% (9/163), endometriosis was the primary indication for the surgical procedure. Thus, to minimize the magnitude of misclassification of the outcome and confounding by indication for hysterectomy, only incident cases that reported a laparoscopic confirmation of their diagnosis were included in the study.

Using laparoscopic confirmation to define endometriosis cases results in a complex relation between endometriosis and fertility status. The baseline prevalence of infertility (defined as attempting to conceive for >12 months without success) in this cohort is higher among those with laparoscopically confirmed endometriosis (20%) compared to those reporting endometriosis without laparoscopic confirmation (4%). Among women with infertility, many may have only been diagnosed with endometriosis during an infertility evaluation. In contrast, women with endometriosis without infertility are more likely to have pain as an indication for laparoscopic evaluation. Because women with endometriosis with infertility may have a higher prevalence of asymptomatic disease secondary to other primary causes of infertility, the risk factors for endometriosis with infertility may differ from those for endometriosis without infertility. Therefore, we conducted analyses stratified by fertility status.

## Assessment of dietary exposures and covariates

Diet was assessed via the semiquantitative FFQ in 1991 and every 4 years thereafter. Women were asked to report their usual intake during the past year on >130 food items. Each question had 9 possible responses, ranging from "never or less than once per month" to "six or more times per day." We calculated the intakes of total and specific types of meat by multiplying the portion size of a single serving of each meat item by its reported frequency of intake. The validity of the questionnaire and of meat intake and related nutrients has been extensively assessed.[10–12] For intake of meats, the correlation coefficients comparing the average of prospectively collected 1-week diet records and the FFQ were 0.67 for chicken without skin, 0.58 for chicken with skin, 0.55 for processed meats, 0.38 for hamburgers, 0.56 for hot dogs, 0.66 for fish, and 0.77 for eggs.[12] For nutrients concentrated in these foods, the correlation coefficients were 0.68 for zinc with supplements, 0.52 zinc from foods alone, 0.71 vitamin B1 with supplements, 0.54 vitamin B1 from foods alone, 0.74 vitamin B12 with supplements, 0.56 vitamin B12 from foods alone, 0.58 iron with supplements, 0.56 iron from foods alone, and palmitic fatty acid 0.70.

Analyses for meat consumption were conducted using the following categories: red meat including processed and organ meats (hot dogs, bacon, sliced processed meat, hamburger, beef/pork/lamb sandwich, pork, beef, liver), unprocessed red meat (hamburger, beef/pork/lamb sandwich, pork, beef, liver), processed red meat (hot dog, bacon and sliced processed meat), poultry (chicken, turkey), fish (canned tuna, dark meat fish, other fish), shellfish (shrimp, lobster, scallops), and eggs.

## Statistical analyses

Participants were followed up from return of the baseline FFQ (1991) until self-