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Review

Risk of colorectal cancer with hysterectomy and oophorectomy: A systematic review and meta-analysis

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HIGHLIGHTS

- Risk of CRC was increased for women undergoing hysterectomy or oophorectomy.
- Given that 300,000 women without susceptibility genes for ovarian cancer or metrocarcinoma undergo oophorectomy or hysterectomy every year, the association of oophorectomy or hysterectomy with increased morbidity of CRC in the entire population has implications for public health guidance.
- Lacking randomized controlled trials, these high-quality cohort studies with large size and high follow-up rate of long-term follow-up offer a good method to assess these associations.
- This meta-analysis is the first to evaluate these controversial results.

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ABSTRACT

Background: Colorectal cancer (CRC) is the second most commonly diagnosed cancer worldwide in females. Sex hormones may play a protective effect in CRC pathogenesis. Ovarian sex steroid levels are reduced in premenopausal women after hysterectomy. Prospective studies have revealed an 80% decrease in serum oestradiol levels after bilateral oophorectomy in premenopausal women. We aimed to elucidate the relationship between hysterectomy or oophorectomy and risk of CRC.

Methods: We estimated relative risk (RR) and 95% confidence intervals (95% CIs) with the meta-analysis. Cochran's Q test and Higgins I^2 statistic were used to check for heterogeneity. Subgroup and sensitivity analyses were performed as were Egger's and Begg's tests and the "trim-and-fill" method for publication bias analysis.

Results: Risk of CRC was increased 30% for women undergoing oophorectomy relative to the general population and 24% with hysterectomy relative to no surgery. The risk was increased 22% with hysterectomy with bilateral salpingoo-ophorectomy as compared with simple hysterectomy. On subgroup analysis, risk of rectal cancer was increased 28% and colon cancer 19% with hysterectomy. Europeans seem to be sensitive to the risk of CRC, with 27% increased risk after hysterectomy. The risk of CRC after oophorectomy gradually increased with age at oophorectomy. The risk was greater with bilateral oophorectomy, with 36% increased risk, than unilateral oophorectomy, with 20% increased risk. Risk was increased 66% with time since oophorectomy 1–4 years as compared with 5–9 and $\geq$ 10 years.

Conclusions: Risk of CRC was increased for women undergoing hysterectomy or oophorectomy. Women with susceptibility genes for ovarian cancer or metrocarcinoma should choose oophorectomy or hysterectomy. For women not at high risk for these cancers, oophorectomy or hysterectomy should not be recommended for increasing the subsequent risk of CRC.

1. Background

Colorectal cancer (CRC), the second most commonly diagnosed cancer and third leading cause of cancer deaths worldwide in females, accounts for an important proportion of the global burden of

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cancer incidence and mortality rates [1]. Primary prevention of CRC should be a preferential task of public health. Smoking, physical inactivity, overweight and obesity, red and processed meat consumption, and excessive alcohol consumption play a part in CRC pathogenesis, as do sex hormones, especially estrogen, and estrogen therapy is used for protection [2] [3]. Morbidity and mortality are higher in men than women [4].

Estrogen, especially oestradiol, has revealed this phenomenon by several mechanisms that include reduced secondary bile acid production, reduced circulating insulin like growth factor-I, stimulating humoral and cell-mediated immune response and inhibiting cell proliferation of colorectal tumors by binding to the estrogen receptor-like ER-β [2,5–8]. The expression of ER-β is lower in tumour tissue than normal colonic mucosa and is inversely related to stage of CRC [9]. Earlier age at natural menopause is related to increased risk of CRC [10]. As well, two prospective cohort studies in the general population revealed no association of testosterone levels and CRC [11,12]. However, androgen deprivation therapy may increase the risk of CRC [13,14]. Observational and experimental studies have revealed that exposure to oral contraceptives and hormone replacement therapy lowers the risk [15–18]. However, case–cohort and case–control studies have shown conflicting results regarding the risk of CRC and endogenous levels of sex steroids in postmenopausal women [19–23].

Hysterectomy is one of the most frequent gynecologic surgeries among women. Overall, 90% of hysterectomies are performed because of benign gynecological conditions such as symptomatic uterine fibroids, endometriosis or unusual uterine bleeding [24–26]. In the United States, about 600,000 women undergo hysterectomy every year [26,24]. In European countries, the prevalence of hysterectomy is highest in Finland (390/100 000 women of any age) [27] and Denmark (360/100 000 women of any age) [28]. Hysterectomy weakens ovarian function by damaging ovarian tissue or compromises the blood supply theoretically, as was shown in prospective studies of women before and after simple hysterectomy [29–31]. Premenopausal women after hysterectomy with ovarian preservation have higher hormone contents, lower ovarian sex steroid levels, and earlier menopause than those without hysterectomy [30,32,33]. The morbidity of breast cancer is reduced by one third after hysterectomy [34,35]. However, in recent studies, hysterectomy increased the risk of CRC [36], whereas previous studies found no association of hysterectomy and CRC risk [37–39].

To reduce the risk of ovarian cancer [40,41] and breast cancer [42–47], bilateral oophorectomy is recommended for benign lesions. Approximately 300,000 women undergo prophylactic oophorectomy each year in the United States. Prospective studies have found decreased serum oestradiol levels by 80% after bilateral oophorectomy in premenopausal women [48]. Postmenopausal woman with ovaries sostenuto secrete abundant testosterone and androstenedione, which is translated into estrogen peripherally [49,50]. Androgen content is reduced by 50% after bilateral oophorectomy in both premenopausal and postmenopausal women [29,48,49,51–53]. However, the relationship between oophorectomy and risk of CRC is still unclear. A positive association was revealed by a few epidemiologic studies [39,42,54], but others [55,42] had negative results.

To elucidate the relationship between hysterectomy or oophorectomy and risk of CRC, we performed a systematic review and meta-analysis to summarize the published epidemiologic evidence. This meta-analysis is the first to evaluate these controversial results.

2. Materials and methods

2.1. Search strategy and study selection

Two authors independently searched PubMed for articles published in English up to June 16, 2016 by using the following key words: ("Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR ((colon[tiab] OR colonic[tiab] OR rectal[tiab] OR rectum[tiab] OR colorect*[tiab] OR large bowel [tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR adenoma*[tiab] OR malignan*[tiab] OR tumour* [tiab] OR tumour*[tiab] OR neoplas*[tiab]))), and ("Ovariectomy"[Mesh] OR ovariectomy[tiab] OR oophorectomy[tiab] OR "Hysterectomy"[Mesh] OR hysterectomy[tiab] OR "Hysterectomy, Vaginal"[Mesh]). Titles, abstracts, full texts and reference lists of all identified reports were reviewed in duplicate by the two authors, and extracted articles were double-checked. Disagreements were resolved by discussion among the three authors. Reference lists from related main studies and review articles were also checked for additional relevant reports.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if 1) participants were from a general population (i.e., not a specific disease group); 2) the exposure of interest was hysterectomy or oophorectomy or their combination; 3) the control group was defined; 4) the outcome of interest was the diagnosis of CRC; 5) articles provided adjusted risk ratio or equivalent risk variables (i.e., hazard ratio, odds ratio), and corresponding 95% confidence intervals (CIs) or data to calculate them. We excluded the following: 1) reviews and letters; 2) duplicate publications; 3) unqualified data; and 4) articles with participants who had a history of cancer before baseline, a family history of ovarian cancer or metrocarcinoma, or reproductive surgery after natural menopause. When two articles appeared to report results with overlapping data, only the data representing the most recent publication or with the larger sample size were included in the meta-analysis. No publications were excluded on the basis of quality, sample size, or other objective criteria relevant to study design and analysis.

2.3. Quality assessment

We evaluated the quality of all reports included by the Newcastle-Ottawa quality assessment scale for cohort studies [56] (http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf). Quality mainly involved 1) selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the study start); 2) comparability (comparability of cohorts on the basis of the design or analysis); and 3) outcome (assessment of outcome, follow-up long enough for outcomes to occur, and adequacy of follow-up of cohorts).

2.4. Data extraction

We extracted data on 1) publication details (first author's name, year of publication and study design); 2) baseline characteristics of the studied population (country, numbers of observation group, cancer, follow-up time, hormone therapy); (3) surgery detail (surgical method, age at surgery, time since surgery); (4) RR of CRC for different gynecological surgeries and 95% CIs. If these data were