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Bilateral Oophorectomy and Rate of Colorectal Cancer A Prospective Cohort Study

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Abbreviations

aRR: adjusted rate ratio

BMI: Body mass index

CI: confidence interval

DAG: Directed Acyclic Graph

DNO: Danish Nurse Organization

HRT: hormone replacement therapy

ICD: International Classification of Disease

RR: Rate ratio

Abstract

Worldwide, colorectal cancer is the second most common cancer and third cause of cancer death in women. Estrogen exposure has been inversely associated with colorectal cancer. Oophorectomy reduces circulating estrogen, but the effect on colorectal cancer remains uncertain. The aim of this study was to examine the association between unilateral and bilateral oophorectomy and subsequent risk of colorectal cancer, and whether this association varied by menopausal status at time of oophorectomy, use of hormone replacement therapy (HRT) at baseline, hysterectomy and baseline body mass index (BMI).

The study included 25,698 female nurses (aged ≥45 years) participating in the Danish Nurse Cohort. Nurses were followed from baseline until date of colorectal cancer, death, emigration or end of follow-up at 31st December 2018, whichever came first. We examined the association between oophorectomy and colorectal cancer (all ages and stratified by menopausal status). The potential modifying effects of hysterectomy, HRT use at baseline and BMI were investigated.

During 542,140 person-years of follow-up, 863 (3.4%) nurses were diagnosed with colorectal cancer. Bilateral oophorectomy was associated with a 79% increased colorectal cancer rate, adjusted rate ratio (aRR) (95% confidence interval, CI): 1.79 (1.33; 2.42). Effect estimates following unilateral oophorectomy also showed higher rate of colorectal cancer, although less pronounced and non-statistically significant (aRR) (95% CI): 1.25 (0.86;1.82). Similar results were seen when stratifying by menopausal status. The association was not modified by baseline HRT use, hysterectomy or BMI.

Oophorectomy was associated with increased rate of colorectal cancer, with highest rates among women with bilateral oophorectomy.

Novelty and Impact

The study is one of the largest studies examining the association between oophorectomy and colorectal cancer in the general population and to determine the modifying effect of HRT and hysterectomy on the association. Oophorectomy at any age increased the rate of colorectal cancer, with highest rate following bilateral oophorectomy. The association was not modified by baseline HRT use or by hysterectomy. These observations are relevant for women considering oophorectomy.

Introduction

Colorectal cancer is the second most diagnosed cancer and the third cause of cancer death in women worldwide [1]. In Denmark, around 2,380 new cases of colorectal cancer were diagnosed each year in women in the period from 2012-2016, representing 13% of all female cancers (excluding non-melanoma skin cancer) and an age standardized incidence rate of 35.8 per 100,000 person-years [2]. Several previous studies have reported associations between ovarian sex hormone exposures and risk of colorectal cancer, with most suggesting that estrogen exposure reduces the risk of colorectal cancer [3,4]. Early menopause which leads to a reduction in ovarian estrogen and progesterone production has been associated with an increased risk of colorectal cancer [5].

Oophorectomy is defined as the surgical removal of one (unilateral) or both (bilateral) ovaries. Bilateral oophorectomy is most often an elective procedure for the management of benign gynaecological conditions (such as chronic pelvic pain or recurrent ovarian cysts) or as risk-reduction in women at high inherited risk of ovarian cancer [6]. Bilateral oophorectomy prior to natural menopause will induce immediate (surgical) menopause with an abrupt cessation of estrogen production [7]. Because post-menopausal ovaries continue to produce sex steroid hormones (primarily androgens which are aromatized to estrogens) at low concentrations, post-menopausal bilateral oophorectomy will also change the endogenous sex steroid environment in postmenopausal women [8,9].

Relatively little is known about the effects of bilateral oophorectomy on the risk of colorectal cancer. One Swedish population-based study (n=195,973) reported that oophorectomy increased the risk of colorectal cancer, with a greater risk after bilateral compared to unilateral oophorectomy [10]. However, data are conflicting and other large prospective cohort studies have shown no association between oophorectomy and colorectal cancer [11–14].

Following pre-menopausal oophorectomy patients are advised to take HRT until around age 50 years to reduce the adverse short and long-term consequences of surgical menopause [15]. However, little is known about the effect of HRT on the association between oophorectomy and colorectal cancer. Two large observational studies investigating the direct association between HRT use and colorectal cancer suggest that HRT reduces risk, and have reported an inverse association between current [16] as well as previous [17] HRT usage and colorectal cancer. However, evidence is conflicting regarding the effect of HRT type and although both of the abovementioned studies found evidence that both combined (estrogen plus progestin) and estrogen-only HRT reduce colorectal cancer risk [16,17], the largest randomized controlled trial of HRT in post-menopausal women demonstrated a reduced risk of colorectal cancer with combined (estrogen plus progestin) but not estrogen-only HRT [18]. This carries clinical implications since oophorectomy is commonly performed at the same time as hysterectomy and subsequent use of HRT would include only estrogen preparations.

Obesity may also increase the risk of colorectal cancer [19], however the association between oophorectomy, obesity and colorectal cancer is unknown. Similarly, hysterectomy alone may increase the risk of colorectal cancer [20] with a non-significant trend for hysterectomy plus oophorectomy to increase colorectal cancer risk compared to hysterectomized women with ovarian conservation [11,12,14].

The aim of this study was to examine the association between unilateral and bilateral oophorectomy and subsequent risk of colorectal cancer, and whether this association varied by menopausal status at time of oophorectomy, use of HRT at baseline, hysterectomy and baseline BMI.

Methods

The Danish Nurse Cohort

This prospective cohort study utilizes the Danish Nurse Cohort established in 1993 with the aim of examining the effects of HRT on long-term health [21]. The cohort study has previously been described

in detail [21]. The cohort comprises female nurses recruited from the Danish Nurse Organization (DNO). The high recruitment rate (95% of all Danish nurses) makes this cohort representative of the Danish nursing workforce in 1993 and thus the general female population aged ≥45 years in terms of cancer risk. The cohort was initiated in 1993, where 23,170 female DNO members (≥45 years) received a questionnaire and 19,898 (86%) responded. In 1999, an additional 8,833 (69%) female nurses were included when the cohort was reinvestigated (including newly invited nurses who turned 45 years in the interim since 1993 (n=8,344) or non-responders from 1993 that were re-invited in 1999 (n=489). A total of 28,731 nurses ≥45 years of age are included in the cohort [21]. At baseline in 1993 or 1999, all newly recruited nurses completed self-administered questionnaires including but not limited to information on lifestyle factors (including smoking, alcohol consumption, physical activity and diet), self-reported height, weight and HRT use. The validity of previous and current self-reported HRT has been shown to be excellent (78.4% and 98.4%, respectively) using the Danish Prescription Registry [22]. All 28,731 nurses who completed a baseline questionnaire were linked to the Danish Civil Registration System [23] holding the unique identification numbers given to all Danish citizens, which enables unambiguous linkage to nationwide health registers.

Colorectal cancer ascertainment

Incident colorectal cancer diagnoses were identified using the International Classification of Disease (ICD) 8 and ICD 10 codes using the Danish Cancer Registry established in 1943 (until 31.12.2017) [24] and in the Danish National Patient Registry (01.01.2018 – 31.12.2018) [25] (supplementary information appendix S1, available online). Nurses were followed from cohort entry (baseline) until date of colorectal cancer, death, emigration or end of follow-up (December 31st, 2018), whichever came first. Nurses were excluded from the study if they had a colorectal cancer prior to baseline, an inactive CPR status or missing covariate data.

Oophorectomy exposure ascertainment

We used the unique identification number to link the cohort participants to the Danish National Patient Registry [25] to identify all included nurses undergoing unilateral and bilateral oophorectomy. Oophorectomy cases were identified from ICD 8 (before 1995) or ICD 10 (from 1995) codes (supplementary information appendix S1, available online) and exact dates of the procedure recorded. Unilateral and bilateral oophorectomy was further subdivided by age at oophorectomy. Oophorectomy before age 51 years was classified as pre-menopausal (surgical menopause) and oophorectomy ≥ age 51 years was classified as post-menopausal. Age 51 years was selected because the median age at menopause in Europe range between 50.1-52.8 years [26]. Dates and procedure codes for hysterectomy was also extracted from the Danish National Patient Register [25] (supplementary information appendix S1, available online).

Co-variate ascertainment

Baseline data on BMI, smoking status, alcohol consumption, physical activity, consumption of fatty meat and use of HRT was obtained from self-administered questionnaires. Family history of cancer, including colorectal cancer, was extracted from the Danish National Patient Registry at baseline [25] (supplementary information appendix S1, available online).

Statistical method

Descriptive statistics (median, 5-95th percentiles or frequencies) were calculated for the total study population and stratified according to colorectal cancer diagnosis, exposure status, menopausal status at the time of bilateral oophorectomy and by included versus excluded nurses.

In a time to event setting we use Poisson regression model to model the rate of colorectal cancer and to estimate rate ratios (RRs) and 95% confidence intervals (CI) for developing colorectal cancer in nurses with oophorectomy (unilateral and bilateral)[27,28]. Follow-up time was split in 5-year intervals by attained age (<50, 51-55, 56-60, 61-65, 66-70, 71-75, 76-80, 81-85, 85-90, 90+) and by calendar

year in 5 intervals (1993-1997, 1998-2002, 2003-2007, 2008-2012, 2013-2018). Attained age and calendar year changed during follow-up period as nurses aged and calendar year progressed. Thus, each nurse may contribute with person-time in multiple age and calendar periods during her follow-up. Attained age and calendar time were included in the Poisson regression model as categorical variables, i.e. assuming piecewise constant rates.

Oophorectomy entered the model as a time-varying variable based on the date of surgical procedure and nurses oophorectomized before baseline entered the model as oophorectomized. Nurses who had a second unilateral oophorectomy performed were counted as bilateral oophorectomized (n=50) from the date of the second unilateral oophorectomy. Hysterectomy was considered a confounder and effect modifier and was also identified using procedure codes and treated as a time-varying variable.

In model 1, we estimated RRs adjusted for attained age and calendar period and in model 2, RRs were further adjusted for BMI (<25, ≥25 kg/m^2), smoking (current, previous, never), alcohol consumption (none, low, moderate, high), family history of any cancer (yes, no), baseline HRT use (ever, never) and hysterectomy (time-varying). The confounders selected for inclusion in the adjusted models were based on a directed acyclic graph (DAG) designed according to a review of the literature of risk factors for oophorectomy and colorectal cancer (Figure S1) (supplementary information, available online). A sub-analysis was conducted in which the main adjusted model 2, was further adjusted for physical activity (low, moderate, high) and consumption of fatty meat (yes, no), this was performed as fatty meat and physical activity are directly associated with colorectal cancer risk but not to oophorectomy and are thus not confounders. The effect of oophorectomy was further evaluated according to menopausal status at the time of oophorectomy (<51/≥51 years as a proxy). The modifying effect of HRT, hysterectomy and BMI on the association between bilateral oophorectomy and colorectal cancer rate using the main adjusted model 2 (but not adjusted for the effect modifier investigated in the model) were tested by likelihood ratio test for interaction. In addition, we repeated

the effect modification analysis of HRT on a sub-population of nurses who had an oophorectomy performed prior to baseline.

As a sensitivity analysis, we repeated the main analysis censoring nurses with breast, ovarian or endometrial cancer +/- three months from date of oophorectomy to exclude nurses having an oophorectomy as part of cancer treatment.

We did a sub-analysis, stratifying according to time since bilateral oophorectomy using the following intervals: <5 years, 5-10 years and ≥10 years.

The GENMOD procedure in SAS version 9.4 was used. All results are presented as RRs with 95% CIs. The significance level was set to 5%.

Results

Basic characteristics

Of the 28,731 recruited nurses, 3,033 were excluded due to previous colorectal cancer at baseline (n=81), an inactive status in CPR (n<5) and/or missing covariate data (n=2,948), leaving 25,698 for final analysis. During 542,140 person-years of follow-up, a total of 863 (3.4%) nurses developed incident colorectal cancer corresponding to an incidence rate of 1.6 per 1000 person-years compared to an incidence rate of 2.4 per 1000 person-years in the background population [2].

All participant characteristics stratified by colorectal cancer status are presented in Table 1. Nurses who developed colorectal cancer were more likely to be overweight, to be current or previous smokers, to never drink alcohol and to be nulliparous. In total, 2,074 (8.0%) nurses had a bilateral oophorectomy, 1,073 (4.1%) had a unilateral oophorectomy, 4,335 (16.9%) had a hysterectomy performed and 7,214 (28.1%) reported use of HRT at baseline. Bilateral oophorectomy (both pre- and post-menopausal) were more frequently performed among nurses with a colorectal cancer after

baseline and nurses with colorectal cancer were more likely to report ever using HRT at baseline compared to nurses without colorectal cancer (Table 1).

Excluded nurses were older at baseline and were less likely to have a normal BMI, to drink >14 units of alcohol/week, to be current smokers, to ever have used HRT and to have had a hysterectomy performed, but more likely to be inactive, to consume fatty meat and to be nulliparous than included nurses (Table S1).

Exposure

Of the 2,074 bilateral oophorectomized nurses, 421 (20.3%) were pre-menopausal at time of oophorectomy and 1,653 (79.7%) were post-menopausal. Pre-menopausal bilateral oophorectomy was more prevalent among current smokers, ever users of HRT at baseline, those hysterectomized, those with colorectal cancer and those younger at first childbirth compared to post-menopausal bilateral oophorectomy. BMI, alcohol, consumption of fatty meat, age at menarche, parity and number of births were similar in both groups (Table S2). The minimum and maximum time from oophorectomy to colorectal cancer diagnosis was 0 and 38 years, respectively with an average time of 15 years (results not shown in tables).

Of the 25,698 female nurses included in the study, 1,073 contributed with person-years after unilateral oophorectomy and 2,074 contributed with person-years after bilateral oophorectomy. Fifty nurses who had a second unilateral oophorectomy performed contributed with person-years for unilateral oophorectomy until the date of their second unilateral oophorectomy, after which they contributed with person-years for bilateral oophorectomy. Obesity (BMI $\geq$ 25), hysterectomy, ever use of HRT and nulliparity were more frequent amongst nurses with an oophorectomy compared to non-oophorectomized nurses. Nurses with bilateral oophorectomy were less likely to have a high physical activity level, to be current smokers or be heavy drinkers compared to nurses with unilateral

oophorectomy and non-oophorectomized nurses. Age, consumption of fatty meat, age at menarche, number of births and age at first birth were similar in all three groups (Table S3).

Colorectal cancer

Bilateral oophorectomy at any age was associated with a statistically significant increased rate of colorectal cancer compared to nurses with preserved ovaries, with an adjusted rate ratio (aRR) (95% confidence interval, CI): 1.79 (1.33;2.42). Unilateral oophorectomy was also positively associated with colorectal cancer, but associations did not reach statistical significance and estimates were weaker than those with bilateral oophorectomy (aRR) (95% CI): 1.25 (0.86;1.82). Further adjustment for physical activity and fatty meat consumption did not change the estimate for bilateral (aRR) (95% CI): 1.78 (1.32;2.40) or unilateral oophorectomy (aRR) (95% CI): 1.25 (0.86;1.82) (Table 2). When censoring nurses with breast, ovarian or endometrial cancer diagnosis +/- three months from date of oophorectomy, results were similar to the main analysis in direction but with a slightly stronger association for bilateral oophorectomy (aRR) (95% CI): 1.87 (1.33; 2.62) (results not shown).

The rate of colorectal cancer among nurses with bilateral oophorectomy remained elevated when subdivided according to whether the procedure was performed in pre-menopausal (aRR) (95% CI): 2.06 (1.25;3.40) or post-menopausal women (aRR) (95% CI): 1.76 (1.27;2.45). Although the numbers with unilateral oophorectomy were small and the findings did not reach statistical significance, colorectal cancer rates also remained elevated regardless of menopausal status and estimates were (aRR) (95% CI): 1.18 (0.73;1.91) for pre-menopausal and (aRR) (95% CI): 1.41 (0.79;2.51) for post-menopausal unilateral oophorectomy (Table 2).

When stratifying according to time since bilateral oophorectomy, the highest rate of colorectal cancer was seen 5-10 years after oophorectomy (aRR) (95% CI): 2.40 (1.32;4.37) compared to nurses with preserved ovaries. The rate ratios were slightly lower after more than 10 years since oophorectomy

(aRR) (95% CI): 1.74 (1.26;2.40), and within 5 years after oophorectomy (aRR) (95% CI): 1.41 (0.56;3.55) (results not shown in tables).

Effect modification

Rates of colorectal cancer were elevated following bilateral oophorectomy compared to nurses with retained ovaries both amongst ever users of HRT at baseline (aRR) (95% CI): 1.59 (1.08;2.33) and never users of HRT (aRR) (95% CI): 1.99 (1.37;2.89). Likewise, rates of colorectal cancer were elevated both among bilateral oophorectomized nurses with hysterectomy (aRR) (95% CI): 1.85 (1.28;2.66) and among bilateral oophorectomized nurses with no hysterectomy (aRR) (95% CI): 1.90 (1.09;3.32) compared to nurses with retained ovaries with and without hysterectomy, respectively. Finally, similar rates were seen with bilateral oophorectomy compared to nurses with ovaries preserved both amongst nurses with BMI ≥25 kg/m^2 (aRR) (95% CI): 2.05 (1.34;3.13) and nurses with BMI<25 kg/m^2 (aRR) (95% CI): 1.67 (1.18;2.37). Neither HRT use, hysterectomy nor BMI≥25 kg/m^2 statistically significantly modified the association between bilateral oophorectomy and colorectal cancer (Table 3). Similarly, there were no statistically significant modifying effects of HRT, hysterectomy and BMI on the association between unilateral oophorectomy and colorectal cancer although this was based on fewer cases (results not shown).

Results were similar in direction and magnitude when repeating the effect modification analysis of HRT on a sub-population of nurses with oophorectomy prior to baseline (results not shown).

Discussion

In this large prospective cohort study, we observed a 79% and 25% increased rate of colorectal cancer following bilateral and unilateral oophorectomy, respectively, when compared to nurses with preserved ovaries. This observed increased rate of colorectal cancer was not modified by menopausal status at the time of bilateral oophorectomy. Since oophorectomy reduces endogenous estrogen

exposure, particularly when performed prior to natural menopause, our findings are consistent with previous preclinical [29] and clinical studies [30] demonstrating an inverse association between estrogen exposure and risk of colorectal cancer.

To date, only few epidemiological studies have investigated the association between oophorectomy and colorectal cancer and the results are inconclusive. One Swedish national study previously reported an increased risk of colorectal cancer amongst women all ages following bilateral oophorectomy compared with women from the general population, consistent with our observations [10]. This was the only previous study to determine the association between oophorectomy and colorectal cancer independently of hysterectomy. All other previous studies have investigated the joint effects of hysterectomy and concurrent oophorectomy on the risk of colorectal cancer and have reported either significant increased risk [13] or non-significant trends towards increased risk [11,14].

Pre-menopausal bilateral oophorectomy will induce surgical menopause and a substantial reduction in endogenous estrogens [31]. After menopause, ovarian estradiol production is low, but estrogens are produced in smaller amounts through the aromatization of ovarian androgens in fatty tissues [32]. Post-menopausal bilateral oophorectomy further reduces endogenous estrogens [33]. We observed a slightly higher rate of colorectal cancer following pre-menopausal bilateral oophorectomy compared to post-menopausal bilateral oophorectomy. In contrast, for unilateral oophorectomy, the rate of colorectal cancer was greater for post-menopausal nurses than for pre-menopausal nurses. However, this may be explained by imprecision in estimates as the number of nurses with unilateral oophorectomy was very small, and for both unilateral and bilateral oophorectomy confidence intervals for pre- and post-menopausal procedures were largely overlapping. Several other studies of colorectal cancer risk have stratified analyses according to menopausal status at time of oophorectomy with inconclusive findings. For example, one register-based cohort study found that both pre- and post-menopausal bilateral oophorectomy were associated with increased risk of colorectal cancer, but with greater risk

among post-menopausal women [10]. Another large prospective cohort study in African American women reported no association between bilateral oophorectomy and colorectal cancer risk in either pre- or post-menopausal women, but relied on self-report of exposure information potentially resulting in misclassification [13]. Yet another large prospective cohort study, the Cancer Prevention Study-II Nutrition Cohort reported a non-significant reduced risk of colorectal cancer following pre-menopausal bilateral oophorectomy with hysterectomy, but a statistically significant increased risk following post-menopausal bilateral oophorectomy with hysterectomy [14]. Finally, The Women's Health Initiative Observational Study reported a non-significant increased risk of colorectal cancer after premenopausal bilateral oophorectomy at the time of hysterectomy but no association between postmenopausal oophorectomy and colorectal cancer risk. However, this study was small and had limited statistical power which may have failed to detect small differences [12].

Only one previous study has examined the association between unilateral oophorectomy and risk of colorectal cancer and found a statistically significant increased risk [10], supporting our observation of a trend towards increased colorectal cancer risk following unilateral oophorectomy, despite the low numbers.

Further evidence to support the hypothesis that estrogen is protective against colorectal cancer comes from studies demonstrating that estrogen containing HRT reduces risk of colorectal cancer in post-menopausal women [17,34]. We did not observe a strong modifying effect of HRT use at baseline on the association between oophorectomy and colorectal cancer. Among HRT users, bilateral oophorectomy was associated with increased rate of colorectal cancer compared to a referent group of nurses with intact ovaries. However, among non-HRT users, the rate of colorectal cancer was increased among bilateral oophorectomized women compared to women with preserved ovaries, suggesting that HRT (estrogen) is protective against colorectal cancer. In contrast, the cohort study in African American women observed a non-significant increased risk of colorectal cancer among HRT users after

premenopausal bilateral oophorectomy [13]. However, our study including predominantly Caucasian women and risk factors for colorectal cancer may differ by racial group [35].

Differentiating the separate effects of oophorectomy and hysterectomy on rates of colorectal cancer is complicated by the fact that oophorectomy is often concurrent with hysterectomy. Three previous prospective cohort studies have reported trends towards an increased risk of colorectal cancer after hysterectomy with oophorectomy compared to women with hysterectomy and ovarian conservation [11,12,14]. In our study, 81.3% of nurses with bilateral oophorectomy had also had a hysterectomy. Hysterectomy did not significantly modify the association between oophorectomy and colorectal cancer, and when stratifying our main analyses by hysterectomy status we still observed higher rates of colorectal cancer in oophorectomized nurses compared to nurses with ovarian conservation within the strata of hysterectomized women. A similar association was seen among nurses with bilateral oophorectomy and no hysterectomy compared to nurses with intact uteri and ovaries (estimates were similar in direction and magnitude). Together, our data suggest that oophorectomy with hysterectomy increases colorectal cancer rate compared to hysterectomy alone.

Extensive body fat is a well-established risk factor for colorectal cancer [36,37] possibly due to higher levels of serum insulin [38]. This study is the first to investigate the effect of BMI on the association between oophorectomy and colorectal cancer rate. However, when stratifying analyses by overweight, rates of colorectal cancer were similar in both strata.

Strengths and limitations

Our study has several strengths. Information regarding age at oophorectomy, deaths, colorectal cancer as well as disappearance and emigration has been collected in nationwide registers in Denmark for the whole population for many decades. These registries are known for their quality and validity, and they gave us the ability to answer questions about exposures and health outcomes that cannot be

addressed in most other countries. In each registry, using the unique number allowed accurate linkage between registries [23]. Healthcare is publicly fully reimbursed in Denmark and thus socio-economic factors would potentially play a smaller role determining whether a person seeks medical care when compared to countries with pay-healthcare leading to reduced bias, although we do acknowledge that higher social status would still partially impact whether a person seeks medical care regardless of the healthcare system. The Danish population is very genetically homogenous and 98% Caucasian, thus we do not expect ethnicity to affect the associations we find, on the other hand our findings may not be generalizable to non-Caucasian women.

Another advantage of this study includes the objective case ascertainment (unilateral-/bilateral oophorectomy) and the assessment of outcome incidence based on the Danish registries. However, if a nurse had her oophorectomy or hysterectomy procedure before NPR was initiated in 1977 or while living abroad it would not be recorded in NPR. Furthermore, the Danish Nurse Cohort provides well characterized baseline information including BMI, parity, age at menarche and oral contraceptive use. All Danish nurses who were members of the Danish Nursing Organization (95% of all nurses) were invited to participate in this cohort, and the participation rate was high, thus the study had little risk of selection bias as we do not expect that participation was motivated by any knowledge of the unilateral- or bilateral oophorectomy procedure or colorectal cancer during follow-up.

One of the primary limitations of our study includes a relatively low number of nurses with pre-menopausal oophorectomy (n=421) and post-menopausal oophorectomy (n=1,653) of which only 20 and 62 developed colorectal cancer, respectively. This limits the statistical precision when subdividing according to menopausal status and assessing the effect modification. Secondly, menopausal status was defined by age as a proxy for menopausal status and not by actual menopausal status at time of oophorectomy potentially causing some misclassification of menopausal status. Additionally, we cannot exclude residual confounding by use of 5-year age categories. Furthermore,

confounder variables, including HRT use, were obtained from self-administered questionnaire at baseline and may have changed during the mean 25-year follow-up period. Although we adjust for *a priori* determined confounder, we cannot exclude the possible impact of unknown factors. In addition, there are numerous potential mechanisms by which oophorectomy may influence the risk of colorectal cancer. It is not possible to account for all these factors, thus residual confounding or other confounding cannot be ruled out. However, we did a sub-analysis with further adjustment for physical activity and consumption of fatty meat which are known risk factors for colorectal cancer [39], but that did not change the estimates. Also, endometriosis has been associated with a 13-fold increased risk of colorectal cancer [40], thus it cannot be excluded that endometriosis is a potential modifier on the association between bilateral oophorectomy and colorectal cancer. But due to limited statistical power, we were unable to investigate the potential modifying effect of endometriosis on the association.

The Danish Nurse Cohort was established to explore the effects of HRT on long-term health [21], and we applied the individual baseline questionnaire data provided by nurses on their HRT use. Although the validity of the self-reported HRT use has been investigated [22] and specificity is high (98.4%), prescription registry data would have provided more granularity around type (estrogen only vs combined), dose, duration of use and especially timing. However, utilizing the Danish Prescription Registry was not feasible as it was initiated after cohort recruitment. Moreover, using baseline HRT we cannot exclude the possibility of misclassification of nurses who have started HRT after baseline, and we cannot determine if HRT was used prior to or after oophorectomy was performed.

Finally, we do not have information about pathogenic variants such as Lynch or BRCA 1 or 2, thus it is not possible to identify the reason for oophorectomy. Hence, it cannot be determined whether oophorectomy was performed as a risk reduction or treatment for cancer.

Conclusion

In a large and well characterized cohort of Danish Nurses we found a positive association between oophorectomy and risk of colorectal cancer. Women who had bilateral oophorectomy had highest rates of colorectal cancer, and this association was not modified by use of HRT at baseline, hysterectomy or overweight.

Additional information

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Conflict of interest

All involved authors declare no conflicts of interest and no other disclosures.

Data availability Statement

Data used in the present study is governed and maintained centrally by the Danish Data Health Authority and data access is regulated by EU General Data Protection Regulations (GPDR). Anonymized data can be accessed after approval by the Danish Data Health Authority and the Danish Data Protection Agency. Further details and other data that support the findings of this study are available from the corresponding author upon request.

Ethics Statement

The present study is approved by the Danish Data Protection Agency (J.nr. VD-2018-451, suite nr. 06707) and the nurses who were included in the Original Danish Nurse Cohort provided informed written consent and the original inclusion to the Danish Nurse Cohort was approved by the local Danish Ethical committee (J.nr. BFH-2019-001, suite nr. 06102).

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Table 1: Person-related descriptive characteristics for the 25,698 female nurses (Danish Nurse Cohort), stratified by colorectal cancer.

	Colorectal cancer	
	Yes (n=863)	**No (n=24,835)**
Baseline characteristics		
Age (years), median (5^{th}-95^{th} percentile)	55 (45; 72)	50 (44; 70)
Body Mass Index, (kg/m^2), n (%)		
BMI <18.5	18 (2.1)	632 (2.5)
BMI 18.5-24.9	578 (67.0)	17,119 (68.9)
BMI 25-29.9	209 (24.2)	5,677 (22.9)
BMI >30	58 (6.7)	1,407 (5.7)
Physical activity, n (%)[a]		
Low	62 (7.2)	1,670 (6.7)
Moderate	603 (69.9)	16,310 (65.7)
High	178 (20.6)	6,611 (26.6)
Missing	20 (2.3)	244 (1.0)
Smoking status, n (%)		
Never	258 (29.9)	8,479 (34.1)
Previous	276 (32.0)	7,621 (30.7)
Current	329 (38.1)	8,735 (35.2)
Alcohol consumption, (drinks/week), n (%)[b]		
None	177 (20.5)	3,915 (15.8)
Low drinker (<7)	304 (35.2)	9,170 (36.9)
Moderate drinker (7-14)	189 (21.9)	6,078 (24.5)
Heavy drinker (>14)	193 (22.4)	5,672 (22.8)
Consumption of fatty meat, n (%)[a]	102 (11.8)	2,426 (9.8)
Age at menarche, n (%)		
<12	68 (7.9)	1,978 (8.0)
≥12	795 (92.1)	22,857 (92.0)
Nulliparous, n (%)	149 (17.3)	3,537 (14.2)
Number of births[c], median (5^{th}-95^{th} percentile)	2 (1; 4)	2 (1; 4)
Age at first birth[c], median (5^{th}-95^{th} percentile)	26 (21; 35)	25 (21; 34)
Hormone replacement therapy, n (%)		
Ever	273 (31.6)	6,941 (28.0)
Never	590 (68.4)	17,894 (72.0)
Time-varying variables, ascertained during follow-up		
Hysterectomy, n (%)	137 (15.9)	4,198 (16.9)
Bilateral oophorectomy, n (%)		
Pre-menopausal	20 (2.3)	401 (1.6)
Post-menopausal	62 (7.2)	1,591 (6.4)
Unilateral oophorectomy, n (%)		
Pre-menopausal	21 (2.4)	708 (2.9)
Post-menopausal	12 (1.4)	332 (1.3)

[a] Physical activity and consumption of fatty meat were not included in the main complete case analyses (models 1 and 2).

[b] Including beer (regular and strong), wine (red and white) and liquor

[c] Among parous women

Table 2: Rate ratios (RRs) and 95% confidence intervals (CIs) of colorectal cancers in nurses with oophorectomy (at all ages and stratified by age (< 51 and ≥ 51 years) at time of oophorectomy as a proxy of menopausal status) from the Danish Nurse Cohort (n=25,698) compared with referent women with ovaries preserved.

		Rate ratios (95% confidence interval)		
	N (cases/person-years)	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Oophorectomy*				
Ovaries preserved	753/496,832	1 (reference)	1 (reference)	1 (reference)
Unilateral	33/18,713	1.22 (0.84;1.75)	1.25 (0.86;1.82)	1.25 (0.86;1.82)
Pre-menopausal	21/14,049	1.16 (0.72;1.85)	1.18 (0.73;1.91)	NA
Post-menopausal	12/4,664	1.34 (0.76;2.38)	1.41 (0.79;2.51)	NA
Bilateral	82/26,595	1.71 (1.36;2.16)	1.79 (1.33;2.42)	1.78 (1.32;2.40)
Pre-menopausal	20/8,354	1.93 (1.24;3.01)	2.06 (1.25;3.40)	NA
Post-menopausal	62/18,241	1.66 (1.27;2.16)	1.76 (1.27;2.45)	NA

*Oophorectomy exposure status entered the Poisson model as a time varying variable

[a]Adjusted for attained age and calendar period with log-transformed person-years as the offset by stratifying the person time into five-year intervals for age (<50, 51-55, 56-60, 61-65, 66-70, 71-75, 76-80, 81-85, 85-90, 90+), calendar period into five groups (1993-1997, 1998-2002, 2003-2007, 2008-2012, 2013-2018) and mutual adjustment for oophorectomy (unilateral and bilateral).

[b]As for model 1, with further adjustment for body mass index (<25, ≥25 kg/m^2), smoking status (current, previous, never), alcohol consumption (none, low, moderate, high), family history of cancer (yes, no), hormone replacement therapy (ever, never) and hysterectomy (time-varying).

[c]As for model 2 with further adjustment for physical activity (low, moderate, high) and consumption of fatty meat (yes, no).

Table 3. Effect modification of the association between bilateral oophorectomy (all ages) and colorectal cancer rate by hormone replacement therapy (HRT), hysterectomy and BMI. Women with both ovaries preserved served as reference group

Effect modifier	Bilateral oophorectomy	Cases (person-years)	RR (95% CI)[a]	P-value*
- HRT				
	No	365,304	1 (reference)	*0.35*
	Yes	11,938	1.99 (1.37;2.89)	
+ HRT				
	No	131,528	1 (reference)	
	Yes	14,658	1.59 (1.08;2.33)	
- Hysterectomy				
	No	452,446	1 (reference)	*0.93*
	Yes	3,798	1.90 (1.09;3.32)	
+ Hysterectomy				
	No	44,385	1 (reference)	
	Yes	22,797	1.85 (1.28;2.66)	
BMI <25				
	No	356,596	1 (reference)	*0.41*
	Yes	18,483	1.67 (1.18;2.37)	
BMI ≥25				
	No	140,235	1 (reference)	
	Yes	8,112	2.05 (1.34;3.13)	

[a]Adjusted for attained age and calendar period, body mass index (<25, ≥25 kg/m^2), smoking status (current, previous, never), alcohol consumption (none, low, moderate, high), family history of any cancer (yes, no), hormone replacement therapy (ever, never), hysterectomy (time-varying) and unilateral oophorectomy. But with no adjustment for the interaction variable.
*Test of the null hypothesis using a likelihood ratio test

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Oestrogen exposure has been inversely associated with risk of colorectal cancer. While oophorectomy reduces circulating oestrogen, its impact on colorectal cancer risk remains uncertain. This study is one of the largest studies to examine the association between oophorectomy and colorectal cancer in the general population and to assess the potential modifying effects of hormone replacement therapy and hysterectomy. The results show that oophorectomy at any age increases the rate of colorectal cancer, with the highest rate found following bilateral oophorectomy. Neither baseline hormone replacement therapy or hysterectomy modified this association. These observations are relevant for women considering oophorectomy.