Impact of endometriosis on risk of further gynaecological surgery and cancer: a national cohort study

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Running title: Long-term surgical & cancer risk in women with endometriosis

Abstract

Objective: To evaluate the long term risk of further gynaecological surgery and cancer in women with endometriosis

Design: Cohort study

Setting: Scotland

Participants: 281,937 women with nearly 5 million person years (4,923,628) of follow up from 1981 to 2010

Methods: In this national population based study we compared 17,834 women with a new surgical diagnosis of endometriosis with 83,303 women with no evidence of endometriosis at laparoscopy, 162,966 women who underwent laparoscopic sterilisation and 17,834 age-matched women from the general population. Cox proportional hazards regression was used to calculate crude and adjusted Hazards ratios with 95% Confidence Intervals.

Main outcome measures: Risk of further gynaecological surgery, number and type of repeat surgery and time to repeat surgery from the diagnosis of endometriosis. Cancer outcomes included subsequent risk of all cancer, gynaecological and non – gynaecological cancers.

Results: Women with endometriosis had a significantly higher risk of further surgery when compared with women with no evidence of endometriosis at laparoscopy (HR 1.69, 95% CI 1.65-1.73), women who had undergone laparoscopic sterilisation (HR 3.30, 95% CI 3.23-3.37) and age-matched women from the general population (HR 5.95, 95% CI 5.71-6.20). They also have an increased risk of ovarian cancer when compared with general population counterparts (HR 1.77, 95% CI 1.08-2.89) or those with laparoscopic sterilisation (HR 1.75, 95% CI 1.26-2.45).

Conclusion: Women with surgically diagnosed endometriosis face an increased risk of multiple surgery. They have a higher chance of developing ovarian cancer in comparison with the general population and women with laparoscopic sterilisation.

Key words: Endometriosis, recurrent surgery, hysterectomy, cancer

Tweetable abstract: Women with endometriosis face an increased risk of recurrent surgery and developing ovarian cancer.

Introduction

Endometriosis is a chronic gynaecological condition which affects 2-10% of women of reproductive age and 30-50% of women with pelvic pain and infertility.(1) It is associated with impaired quality of life and constitutes a significant socioeconomic burden.(2) (3) The recurrence of pain is common after both medical and surgical treatment of endometriosis with reported rates varying from 30% to 50% at five years.(4) Surgery remains the mainstay for the diagnosis and treatment of endometriosis. Women often undergo multiple operations in an attempt to alleviate the symptoms of pain. Hysterectomy with removal of both ovaries is a recognised surgical option when alternative treatments have failed and fertility is no longer a priority. Studies on recurrence after treatment for endometriosis (5-9) have predominantly focussed on short to medium term outcomes and not reported on the risk or nature of further surgery. Till date there have been no studies on large national cohorts with adequate length of follow up to evaluate the risk of future surgery after the diagnosis of endometriosis.

Apart from the symptoms of pain and infertility, another area of concern is a potential link between endometriosis and some cancers. The association between endometriosis and ovarian cancer appears to be the most consistent, though findings regarding other gynaecological and non-gynaecological cancers are conflicting.(10-12) The existing literature is not without limitations. A vast majority of studies relied on a self-reported diagnosis of endometriosis (13-17) or focussed on cancer risks in specific subgroups such as infertile (18-20) or postmenopausal women. (14)

The natural history of endometriosis is poorly understood. An improved understanding of the long-term sequelae of endometriosis is needed to allow better counselling of women, inform healthcare professionals and assist with health services planning. We therefore conducted a study to explore the impact of endometriosis on the risk of recurrent surgery and subsequent development of cancer.

Material and Methods

A cohort study using Scotland wide anonymised linked data from 1981 to 2010 was conducted. All women with a new diagnosis of endometriosis (ICD 9 and 10 codes of 617 and N80 respectively) between 1981 and 2009 confirmed by either a laparoscopy or laparotomy comprised our exposed cohort. The current definition and criteria for diagnosis of endometriosis(1) means that the control group can only be reliably identified by a negative laparoscopy. This makes selection of an ideal population based unexposed cohort challenging as it is not possible to subject healthy asymptomatic women to an invasive surgical procedure. In the absence of an ideal comparison group, three unexposed cohorts were selected. The first unexposed cohort (A) consisted of women who did not have any evidence of endometriosis at a diagnostic laparoscopy during the same time period. These women had a diagnostic laparoscopy for the investigation of either pelvic pain or infertility or both. Women undergoing laparoscopic sterilisation between 1981 and 2009 constituted the second unexposed cohort (B). The third unexposed cohort (C) was derived from the general population in a 1:1 ratio and included a random sample of women matched to the endometriosis cohort by the year of birth and the year of entry into the study. All women were followed up to explore long term risks of future gynaecological surgery or development of cancer up till December 2010. Women found to have cancer at the time of index surgical procedure or those with a symptom based diagnosis of endometriosis in the absence of surgical confirmation were excluded from the analysis.

The date of diagnosis of endometriosis (laparoscopy or laparotomy) or the date of negative laparoscopy or laparoscopic sterilisation was used as the index date (starting point for follow up time) to estimate the future risk of gynaecological surgery or cancer. For the matched general population group, the date of diagnosis of endometriosis was used as the index date for each matched participant.

Data for this study were extracted from the Scottish Morbidity Records database held by the Information Services Division (ISD) of the National Health Services Scotland. Clinical and demographic data on all in-patient and day case activity from hospitals across the whole of Scotland are routinely

collected and stored as Scottish Morbidity Records (SMR01). Diagnoses are recorded using the International Classification of Diseases (ICD) 9 and 10 codes and operations are recorded using the Classification for Surgical Operations and Procedures (OPCS) codes. ISD also holds the Community Health Index (CHI) register which is a population register of all individuals registered with a general practice in Scotland. It is used for healthcare purposes and screening programmes. National Data Standards are employed to ensure that healthcare data stored by ISD is of high quality. The data are collected throughout Scotland according to the same classifications and rules and interchanged between systems consistently, robustly and securely. The SMR register is subject to regular quality checks. For over 20 years now and throughout this time the accuracy rate of Main Condition and Main Operation/Procedure has remained relatively stable at around 88% and 94% respectively. Further information can be accessed from http://www.isdscotland.org.

Women with endometriosis, unexposed cohort A (negative laparoscopy) and unexposed cohort B (laparoscopic sterilisation) were identified from the hospital discharge database (SMR01). Women in the unexposed cohort C (general population) were obtained from the CHI register. Baseline information on age and socio-demographic characteristics was extracted for all study participants. Social class was recorded using Carstairs deprivation scale by ISD, where Class V represents the most deprived category.(21) Data on variables such as parity, smoking status, menstrual factors (age at menarche, duration and length of menstrual cycle), use of hormonal contraception, body mass index (BMI), family history and ethnicity, site and stage of endometriosis were either not available or largely missing. Prescription data were only available for the last two years (2009-2010) in our 30-year long study.

Records from the hospital discharge database (SMR01) were linked internally and to the CHI population register to evaluate future gynaecological surgery outcomes and to the Scottish Cancer Registry to determine cancer outcomes in women from the exposed and unexposed groups. Data were

also linked to the General Registry of Births and Deaths in Scotland to identify those women who died in the follow up time period. The data linkage process is illustrated in **Figure 1**.

The long term gynaecological outcomes evaluated were the number and type of repeat gynaecological surgical procedures, time to first repeat surgery and time to hysterectomy from the diagnosis of endometriosis. Gynaecological operations were subdivided into 11 categories as per OPCS classification **(Appendix S1).** The surgical categories evaluated included repeat diagnostic laparoscopy, laparoscopic operations to peritoneum, ovarian surgery, excision of adnexa (unilateral or bilateral), hysterectomy, adhesiolysis, hysteroscopic procedures (including endometrial ablations), pelvic organ prolapse surgery, cystoscopy, and urinary incontinence surgery. All remaining gynaecological procedures, not included within the above ten categories were classed as 'other gynaecological surgery'.

The cancer outcomes explored were the site of cancer and time to first primary cancer. The site of cancer was defined as per International Classification of Disease (ICD) codes **(Appendix S2)**. The cancers were classified as gynaecological and non-gynaecological cancers. Amongst the non-gynaecological cancers, data were extracted separately for breast and gastrointestinal cancer which may have biologically plausible links to endometriosis and are two of the most common cancers in women in Scotland.(22)

SPSS version 21.0 for Windows (SPSS Inc. Chicago, IL, USA) was used for analysis of data. Descriptive statistics [frequencies and percentages; mean and standard deviation (SD); median and interquartile range (IQR) as appropriate] were used to summarise each of the baseline characteristics (age, sociodemographic status and duration of follow up), gynaecological surgery and cancer in the endometriosis and each of the unexposed groups.

Univariate comparisons (Chi squared test for categorical variables, t-test for parametric distributions and the Mann-Whitney test for non-parametric distributions) between the endometriosis group and

each of unexposed groups were carried out as appropriate. Data were adjusted for age and social class to perform multivariate analysis. For the gynaecological outcomes, results were also adjusted for the year of laparoscopy to accommodate for the change in practice, laparoscopic techniques and management of endometriosis over the three decades. Generalised linear models with Poisson log link were constructed to calculate the crude and adjusted incident rate ratios (IRR) with 95% Confidence Intervals (CI) for the number of repeat surgical procedures with an offset for the follow up period. Cox proportional hazards regression was used to examine the time to first repeat surgery, time to hysterectomy and time to development of subsequent cancer from the index date amongst the exposed and each of the unexposed cohorts. Data were presented as crude and adjusted Hazard ratios (HR) with 95% Confidence Intervals.

Data checks identified that the information on social class in the unexposed cohort C was not missing at random. As nearly 70% of women from this group had no hospital contact during the follow up period, information on social class (routinely extracted from the hospital discharge database) was unavailable for these women. Adjusting for social class in the multivariate analysis for this group would bias the results as 70% of women with missing data would be excluded. Given that the general population controls were matched by the year of birth and follow up duration, only univariate analysis was performed for the gynaecological and cancer outcomes when comparing the women with endometriosis with those from the general population.

Results

A total of 42,092 women in Scotland were diagnosed for the first time with endometriosis between 1981 and 2009, as determined by the ICD codes. Of these, only 17,834 women, who had a surgical confirmation of endometriosis at laparoscopy or laparotomy were included in our exposed cohort, with a follow up period of 238,793 person years. The unexposed cohorts A and B comprised 83,303 women with a negative laparoscopy and 162,966 women who had a laparoscopic sterilisation during

the same time period with a follow up of 1,412,696 years and 3,033,703 years respectively. The general population cohort included 17,834 women with a follow up of 238,436 years.

The baseline characteristics of the women with endometriosis and the unexposed cohorts are shown in **Table 1**. Women with endometriosis were significantly older [mean age (SD) of 32.1 (7.3) years] than those who had no evidence of endometriosis at a diagnostic laparoscopy [30.8 (8.5) years] but younger than the laparoscopic sterilisation group [32.9 (5.50 years]. Women with endometriosis belonged to a more affluent social class compared to the other three unexposed groups. The median follow up duration for the endometriosis and the general population cohort was 13.1 years, the negative laparoscopy cohort 17.4 years and the laparoscopic sterilisation group 19.1 years respectively.

Gynaecological outcomes

As shown in **Table 2**, the incidence of subsequent gynaecological surgery was significantly higher in women with endometriosis (n = 11,052; 62%) when compared with women with no evidence of endometriosis at laparoscopy (n = 42,136; 50.6%), women who had undergone laparoscopic sterilisation (n = 58,704; 36%) and age-matched women from the general population (n = 2,907; 16.3%). The median (IQR) time for a second surgical procedure (after the initial diagnostic operation) for the endometriosis group was less than two years [1.8 (0.8, 4.6)] – which was significantly shorter than the corresponding period in women in the three unexposed groups. Half of all women with endometriosis had undergone repeat surgery within 5.5 years.

Nearly 1 in 5 women with endometriosis had a subsequent hysterectomy (n = 4,049; 22.7%) which was significantly higher than the 1 in 10 risk in women who had undergone laparoscopy with no evidence of endometriosis (n = 8,825; 10.6%), laparoscopic sterilisation (n = 17,845; 11%) or 1 in 50 chance in age-matched women from the general population (n = 397; 2.2%). Women with endometriosis appeared to have hysterectomy at a much younger age with a median time to hysterectomy of 2 years after diagnosis when compared to 7.4 years in the negative laparoscopy group

and 8.8 years in the laparoscopic sterilisation group following their primary surgery. The incidence of different types of gynaecological procedures in each group of women is shown in **Table S1**. With the exception of pelvic organ prolapse and urinary incontinence surgery, women with endometriosis were much more likely to have all other kinds of gynaecological operations.

Women with endometriosis were also at a higher risk of multiple repeat surgical procedures. **Table 2** shows the incident rate ratios (IRR) for the number of operative procedures and the hazards ratios for time to first repeat surgery and hysterectomy in women with endometriosis. After allowing for the duration of follow up, and adjusting for age, socio-economic status and the year of initial laparoscopy, the adjusted IRR (95% CI) for the number of subsequent operations was 1.67 (1.65, 1.69), 2.74 (2.71, 2.78) and 3.03 (2.95, 3.13) when compared with the unexposed groups A, B and C respectively. The risks of repeat surgery and hysterectomy were significantly increased in women with endometriosis with adjusted HRs (95% CI) of 1.69 (1.65, 1.73), 3.30 (3.23, 3.37) and 5.95 (5.71, 6.20) for repeat surgery and 3.14 (3.02, 3.26), 4.30 (4.15, 4.50) and 11.74 (10.6, 13.01) for hysterectomy when compared with women with no evidence of endometriosis at laparoscopy, women who had undergone laparoscopic sterilisation or the age-matched women from the general population respectively

Cancer

The proportion of women with endometriosis who developed cancer in the follow up period was 3.8% (n = 669). The corresponding proportions were 5.1% (n = 4,239), 6.3% (n = 10,202) and 3.1% (n = 555) in women with no evidence of endometriosis at laparoscopy, women who have had laparoscopic sterilisation and women from the general population respectively. In the endometriosis group, gynaecological malignancies accounted for 12.4% of all cancers and affected 0.5% of women during the follow up period. The incidence of gynaecological malignancy for the three unexposed cohorts A, B and C were 0.6%, 0.8% and 0.4% respectively. Breast cancer was by far the commonest cancer in all groups accounting for 37.5% of all malignancies and 1.4% of all women in the endometriosis group.

The distribution of various gynaecological cancers, breast and gastrointestinal cancers is shown in **Table 3.**

On multivariate analysis, women with endometriosis were at a significantly higher risk of developing overall future cancer, ovarian cancer and breast cancer when compared to the general population cohort with an adjusted HR (95% CI) of 1.21 (1.08, 1.35), 1.77 (1.08, 2.89) and 1.28 (1.06, 1.54) respectively as shown in **Table 3**. Ovarian cancer was more common in the endometriosis group when compared with women with laparoscopic sterilisation [adjusted HR (95% CI) of 1.75 (1.26, 2.45)]. There were no significant differences in the risk of any cancer, gynaecological malignancies and breast cancer when compared to the negative laparoscopy group.

Discussion

Principal Findings

This Scottish nation-wide study revealed that women with endometriosis to be at a significantly higher risk of multiple further gynaecological surgeries, shorter interval to further surgery and subsequent hysterectomy following their initial diagnosis. A diagnosis of endometriosis is associated with a higher risk of ovarian cancer when compared with the women from general population and those who have undergone laparoscopic sterilisation. There were no significant differences in the risk of any future cancer between women with surgically-diagnosed endometriosis and those with no evidence of endometriosis at laparoscopy.

Strengths and Limitations

With 281,937 women and nearly 5 million (4,923,628) person years of follow up, this is the largest study to describe the long term surgical and cancer outcomes in women with endometriosis. A major strength of the study is the use of a national population-based cohort, access to a complete high

quality national dataset,(23) and a surgical diagnosis of endometriosis. This improves the validity and reliability of our results by minimising misclassification bias.

Identifying an ideal unexposed cohort was difficult. Although not truly representative of community controls, the negative laparoscopy and laparoscopic sterilisation cohorts allowed us to reliably exclude endometriosis. The negative laparoscopy group comprises symptomatic women who were undergoing diagnostic laparoscopy for investigation of pelvic pain and/or infertility. While more like 'community controls', women undergoing laparoscopic sterilisation tend to be very different from those with endometriosis in terms of parity, use of hormonal contraceptives and demographic profile. An interplay of all these factors could potentially influence both the surgical and cancer outcomes. Although it is possible that endometriosis could have been missed at initial laparoscopy, it is worth noting that none of the women in the negative laparoscopy or the laparoscopic sterilisation group had a subsequent diagnosis of endometriosis in up to 30 years of follow up. The third unexposed cohort was truly population based. Any asymptomatic endometriosis however, could not be excluded. The chances of undiagnosed endometriosis in this group is likely to be very low as symptomatic women were excluded.

This study is susceptible to the limitations associated with routinely collected data. Data were missing on confounders such as parity, smoking status, menstrual factors, use of hormonal contraception, body mass index, family history and ethnicity, site and stage of endometriosis and likely unknown confounders specific to the comparison groups. The findings of our study may not be generalisable to other ethnic groups as the study was conducted in Scotland where over 95% of the population is Caucasian.

Interpretation of findings

Whether the return of pain symptoms or the visualisation of endometriotic lesions at a subsequent surgery should be classed as a recurrence is a subject of continuing debate. We chose repeat surgery as a long-term outcome as it marks an objective event in the life of a woman. The literature is sparse

on long-term surgical outcomes in women with endometriosis and the few existing publications(24,25) have much smaller sample sizes with shorter durations of follow up. At 62%, the repeat operation rate following the initial surgical diagnosis in our study (17,834 women with a median follow up of 13.1 years) was higher compared to 51% reported by Cheong et al(24) (486 women with a mean duration of follow up of 5.4 years) and 55% after conservative surgery by Shakiba et al.(25) (120 women with follow up of 7.7 years). In our study women with endometriosis not only had a higher rate (23%) of hysterectomy but also had this procedure at a much younger age (early to mid-thirties). They also had a 1 in 5 risk of removal of one or both ovaries. Bilateral oophorectomy at the time of hysterectomy confers protection against ovarian and breast cancer but is known to be associated with an increase in risk of all-cause mortality, and cardiovascular disease.(26) It is possible that the impact of endometriosis on long term health of the women is iatrogenic and related to the hormonal and/or surgical treatment offered for endometriosis, rather than the disease alone.

Our results suggest that the strength of the association between endometriosis with cancer is less pronounced than is reported in the literature. While a mildly elevated risk of overall cancer was noted when compared to women from the general population [HR (95% CI) of 1.21 (1.08, 1.35)], this association was not evident when compared to the negative laparoscopy or the sterilisation cohort. The choice of comparison group can influence the results as illustrated in our study with three different unexposed cohort. The vast majority of existing smaller studies have analysed cancer risks in specific subsets of women with endometriosis such as infertile women(18-20) and relied on a self-reported diagnosis of endometriosis(14,15,17,27) which carries a high risk of ascertainment bias. The only two large population based cohort studies, with a surgical confirmation of endometriosis were by Melin et al. (28) in the Swedish (1969-2002) women and Wang et al.(29) (2000-2010) in the Taiwanese population. The risk of cancer in the Swedish study(28) was lower than our study with a standardised incident ratio (SIR) and (95% CI) of 1.01 (0.98, 1.05) for overall cancer, 1.08 (1.02, 1.13) for breast cancer and 1.37 (1.14–1.62) for ovarian cancer. The Taiwanese study(29) found a much higher risk of ovarian cancer [adjusted HR (95% CI) of 5.62 (3.46-9.14)] in women with endometriosis,

compared with both the Swedish and the Scottish cohort. The association of endometriosis with ovarian cancer has been studied most extensively. In a meta-analysis of 20 case control and 15 cohort studies, Kim et al.(30) reported a relative risk (RR) with 95% CI of (1.27; 1.21–1.31) in case –control or two-arm cohort studies and SIR (95% CI)) of (1.79; 1.27–2.53) in single arm cohort studies. The risk of ovarian cancer appears to be highest in women with ovarian endometrioma. (31)(32) Our findings corroborate the existing evidence in favour of increased risk of ovarian cancer in women with endometriosis, though the magnitude of effect is much smaller. The association of endometriosis with breast cancer remains controversial,(10,33,34) with studies reporting positive(19,28), negative(16,35) and lack of any association.(12,18,36) The findings across our three cohorts were inconsistent too. Within the same population, differences in statistical analysis can lend different risk estimates.(28,32,37)

Thus, with the exception of ovarian cancer, the association of endometriosis with other cancers remains disputable. A shared pathophysiology may explain a higher risk of ovarian cancer associated with endometriosis (38), including direct transformation from benign to malignant epithelium (39), free iron induced oxidative damage causing DNA mutations (40) and genomic instability similar to cancer cells.(41)

Epidemiological studies are difficult to conduct in endometriosis population due to challenges in defining the onset of disease, a need for laparoscopy to establish the diagnosis, effect of hormonal contraception and pregnancy on the course of disease, difficulties in identifying an ideal comparison group and a lack of standardisation of research design. (42,43) There are huge variations in the diagnosis and management of endometriosis across the world, limiting extrapolation of findings of studies to other populations for health services planning. Multicentre prospective studies using standardised tools for clinical and sample data collection are required to elucidate the effect of varying phenotypes, genetic and environmental influences on symptoms of disease as well as impact on long-term health.

Conclusions

Women with endometriosis are at an increased risk of further surgery. Awareness of the risk of multiple surgical procedures including hysterectomy can be useful in counselling women with a new diagnosis of endometriosis and enable them to make timely reproductive choices. With regards to cancer, the findings of our study are generally reassuring. The elevated risk of ovarian cancer persisted despite higher rates of oophorectomy in women with endometriosis. As the strength of association is low and the confounding influence of parity, use of hormonal contraceptives and other lifestyle factors cannot be excluded, these results should be interpreted with caution. Medical intervention in the form of combined contraceptive pill for prophylaxis, opportunistic salpingectomy or active surgical intervention in women with endometriomata would be recognised measures to reduce the risk of ovarian cancer.

Acknowledgements

We are grateful John Nolan from ISD for data extraction.

Declaration of interests

None of the authors have any competing interests to declare

Contribution to authorship

SB conceived the idea. SB, LS, SoB, KC and DA designed the study and interpreted the data. LS drafted the manuscript and performed statistical analysis with DA. LS, SB, KC, SoB, DA, and AH provided comments and contributed to the development of the final draft of the manuscript.

Ethical approval

Appropriate approvals from the Privacy Advisory Committee of ISD, of the National Health Service, Scotland; North of Scotland Research Ethics Committee (NRES) and NHS Research and Development were sought to conduct the study. As only anonymised data were used, formal ethical approval for this study was waived by the NRES.

Funding

The study was funded by a grant from Chief Scientist Office, Scotland

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