

Incidence of ovarian cancer after hysterectomy: a nationwide controlled follow up

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Objective To estimate the risk of developing ovarian cancer after abdominal (total or subtotal) hysterectomy on benign indication.

Design Prospective historical cohort study with 12.5 years of follow up.

Setting Denmark, nationwide.

Population All Danish women (aged 0 to 99 years) having undergone hysterectomy with conservation of at least one ovary for a benign indication from 1977 to 1981 ($n = 22,135$). Follow up was conducted from 1977 to 1991. The reference group included all Danish women who had not undergone hysterectomy, age-standardised according to the hysterectomy group ($n = 2,554,872$).

Methods Registry data derived from the Danish National Register of Patients (diagnoses and operation codes) and the Civil Registration System (information about general population, including time of death).

Main outcome measures Incidence rate of ovarian cancer, lifetime risk of ovarian cancer, relative risk of ovarian cancer.

Results Seventy-one women developed ovarian cancer on average 7.0 years after hysterectomy and 10,659 women in the reference group had ovarian cancer diagnosed after on average 6.4 years. The incidence rate of ovarian cancer was 0.27 per 1000 person-years in the group that had undergone hysterectomy and 0.34 per 1000 person-years in the general population (age-standardised). The extrapolated lifetime risk of developing ovarian cancer was 2.1% after hysterectomy and 2.7% in the general population (RR 0.78; 95% CI 0.60–0.96).

Conclusions The risk of ovarian cancer is lower among women who have undergone hysterectomy compared with those who have not. The protection seems to decrease with time.

INTRODUCTION

Ovarian cancer is the fourth leading cause of cancer death in Danish women with approximately 500 deaths a year and an incidence of about 600 per year. In Denmark the lifetime risk of ovarian cancer is 2% to 3%.¹ Early detection of ovarian cancer by routine pelvic examination, ultrasound or tumour marker measurements has not reduced the mortality rate which has been unchanged for nearly 40 years. About 75% of all cases of ovarian cancer are diagnosed in postmenopausal women and in Denmark 32% are alive five years after diagnosis.²

Prophylactic oophorectomy in women undergoing hysterectomy is an effective prevention against ovarian cancer. However, controversy exists whether prophylactic oophorectomy should be performed in women with no familial risk of ovarian cancer^{3–5}. In Denmark

about 3000 hysterectomies without bilateral oophorectomy for benign indications were performed every year from 1977 to 1981 on women under the age of 65 years; the cumulated incidence rate for hysterectomy at age 60 years was 17.4%.^{1,6} Among women with ovarian cancer, 4.5% to 18% have previously had a hysterectomy or a laparotomy.¹ Some retrospective case-control studies^{7–15}, as well as one prospective study¹⁶, have reported a reduced incidence of ovarian cancer after hysterectomy.

The aim of this historical cohort study was to estimate the risk of developing ovarian cancer after abdominal (total or subtotal) hysterectomy on benign indication.

METHODS

Every person in Denmark is given a registration number at birth. The data for this study were collected from the Civil Registration System and the Danish National Register of Patients. The former register covers the

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entire Danish population including time of death and the latter discharge diagnoses and operation codes of all hospitalised patients since 1977. The diagnoses were coded at discharge from hospital according to the International Classification of Diseases (ICD-8 183.00–183.09 + 183.99 neoplasma malignum ovarii)¹⁷ and the surgical procedures according to a Scandinavian classification of operations: 61000 subtotal hysterectomy, 61020 total abdominal hysterectomy, 60100/60120 unilateral/bilateral oophorectomy, 60300/60320 unilateral/bilateral salpingo-oophorectomy¹⁸. The histological classification of the tumours was not available in the Danish National Register of Patients.

The study included all women in Denmark who on a benign indication underwent hysterectomy (total or subtotal abdominal) with or without unilateral oophorectomy during the period 1977 to 1981. Women with a gynaecological cancer diagnosis before or at the operation were excluded. The study was conducted as a historical cohort study. All patients were followed from the date of operation until the end of 1991, or on average 12.5 years.

The reference group included all Danish women who had not had a hysterectomy in the period 1977 to 1981, and they were identified through the Civil Registration System. Those who developed ovarian cancer were identified in the Danish National Register of Patients, while time of eventual death was derived from the Civil Registration System.

Validity of hysterectomy diagnoses

The validity of the hysterectomy codes in the Danish National Register of Patients has previously been found to be in accordance with the registration at the local hospitals¹⁹. Other studies have compared the Danish National Register of Patients and the Danish Cancer Registry and have demonstrated that 6% of all cancer patients registered by the Cancer Registry were not registered in the Danish National Register of Patients, while the opposite was found in 5%²⁰.

In this study we identified 30 women (0.14%) who had undergone hysterectomy from 1977 to 1981 and who, later in the follow up period, were registered with another hysterectomy code. One hundred and fifty women (0.46%) who had bilateral oophorectomy performed from 1977 to 1981 were later registered in the observation period with a unilateral or bilateral oophorectomy, or resection of the ovary.

Thus, less than 1% misclassification appears to have occurred for hysterectomy. The few misclassified women with ovarian cancer have probably equally influenced the women who had and those who had not undergone hysterectomy.

Statistical methods

To calculate the incidence rate of ovarian cancer the number of women who leave the population at risk due to either oophorectomy after hysterectomy or to death must be identified. Of 22,135 women who had undergone hysterectomy during the period 1977 to 1981, 294 (1.3%) had both ovaries removed on average 5.0 years after hysterectomy (1470 person-years) (i.e. either one bilateral or two unilateral oophorectomies, or a unilateral oophorectomy after primary hysterectomy with unilateral oophorectomy). Between 1977 and 1991, 1437 women (6.5%) died from causes other than gynaecological cancers, on average 8.2 years after hysterectomy (11,783 person-years). The number of women who had undergone hysterectomy at risk of developing ovarian cancer was accordingly adjusted from 22,135 to 20,333 women at the end of 1991 (254,163 person-years). Since 71 women developed ovarian cancer, on average 7.0 years after hysterectomy, the corresponding follow up period (1977–1991) included in total 267,913 person-years.

In the reference group 14,198 women had both ovaries removed on average 7.1 years after 1 July 1979 (100,806 person-years). The reference group was age-standardised according to the hysterectomy group. Among women who were alive on 1 January 1979, 86,576 died before the end of 1991, on average 8.2 years after 1 July 1979 (709,923 person-years); 10,659 women developed ovarian cancer, on average 6.4 years after 1 July 1979 (68,218 person-years). Thus, 2,443,439 women in the reference group were at risk of developing ovarian cancer at the end of 1991 (30,542,987 person-years). The period 1977–1991 therefore included 31,421,934 person-years of observation.

In the period 1977 to 1981, 8868 women had oophorectomy (unilateral or bilateral) without hysterectomy performed on benign indication. Of these, 86% had unilateral oophorectomy and 70% were below the age of 45 years. If we assume that the frequency of unilateral or bilateral oophorectomy was the same in the period before 1977, less than 0.07% per year will drop out of the population at risk. Therefore, no attempts were made to adjust for oophorectomy before the study period.

The χ^2 test and 95% confidence limits were applied. Level of significance was set at 5%.

RESULTS

From 1977 to 1981 22,135 women had a hysterectomy with conservation of at least one ovary, while 6329 women had bilateral oophorectomy performed together with the hysterectomy. Table 1 indicates the total number and incidence rates according to age of abdominal hysterectomy with and without oophorectomy from 1977 to 1981.

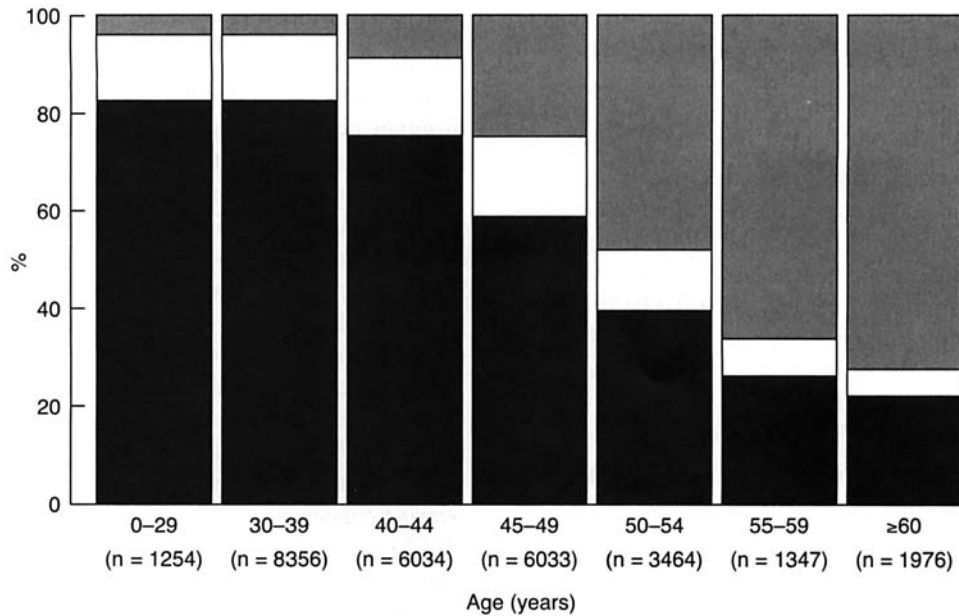


Fig. 1. Hysterectomies on benign indications in Denmark, 1977-1981, according to age. ■ = hysterectomy with bilateral oophorectomy; □ = hysterectomy with unilateral oophorectomy; ▒ = hysterectomy.

Table 1. Average annual incidence rate of total or subtotal abdominal hysterectomy on benign indications in Denmark, 1977-1981. Values are given as *n* (incidence per 100,000 women-years for women in the relevant age group).

| Age (years) | Hysterectomy without oophorectomy | Hysterectomy with unilateral oophorectomy | Hysterectomy with bilateral oophorectomy | Danish female population |
|-------------|-----------------------------------|---|--|--------------------------|
| 0-29 | 1031 (18.9) | 172 (3.0) | 51 (0.9) | 1089,608 |
| 30-39 | 6902 (369.7) | 1138 (61.0) | 316 (16.9) | 373,401 |
| 40-44 | 4555 (630.0) | 960 (132.8) | 519 (71.8) | 144,592 |
| 45-49 | 3550 (520.5) | 999 (146.4) | 1484 (217.6) | 136,420 |
| 50-54 | 1382 (193.9) | 438 (6.4) | 1644 (230.6) | 142,570 |
| 55-59 | 350 (49.1) | 107 (15.0) | 890 (124.9) | 147,593 |
| ≥ 60 | 425 (15.4) | 126 (4.6) | 1425 (51.7) | 551,763 |
| TOTAL | 18,195 | 3940 | 6329 | 2585,947 |

Figure 1 shows the distribution in different age groups of different types of hysterectomies performed for benign indication in Denmark from 1977 to 1981.

From 1977 to 1991, 78,489 women in Denmark had an abdominal (total or subtotal) hysterectomy performed for a benign indication. In the three five-year periods 1977-1981 ($n = 28,464$), 1982-1986 ($n = 26,136$) and 1987-1991 ($n = 23,889$), the total number of operations decreased by 16%. This trend was due to fewer operations before the age of 55 years. The proportion of abdominal hysterectomy without oophorectomy increased from 64% to 71%, abdominal hysterectomy with bilateral oophorectomy decreased from 22% to 18% and hysterectomy with unilateral oophorectomy decreased from 14% to 11%.

Seventy-one women developed ovarian cancer on average 7.0 years after the hysterectomy. Forty-five of the 71 patients (63%) with ovarian cancer died on

average 8.9 years after hysterectomy and 2.2 years after the ovarian cancer was diagnosed (Table 2). In the reference group, 8562 women developed ovarian cancer on average 6.4 years after January 1979 and 6265 patients (73%) died on average 1.4 years after the ovarian cancer was diagnosed. When the reference group was age-standardised according to the hysterectomy group, the number of ovarian cancer cases was 10,659.

Table 3 shows the incidence rate of ovarian cancer among women who had an abdominal hysterectomy performed from 1977-1981 and in the reference group.

The crude incidence rate of ovarian cancer increased with time; 1977-1981: 0.18 per 1000 person-years, 1982-1986: 0.23 per 1000 person-years and 1987-1991: 0.33 per 1000 person years (χ^2 test; $P < 0.001$). The corrected incidence rate of ovarian cancer for the period 1977 to 1991 was 0.27 per 1000 person-years. Anticipating an unchanged incidence rate in the following

Table 2. Number and age-distribution among women with ovarian cancer after abdominal hysterectomy on benign indication in Denmark, 1977–1981 followed until 1991. Values are given as *n*.

| Age (years) | Hysterectomy | Ovarian cancer diagnosed | | | | Death of ovarian cancer |
|-------------|--------------|--------------------------|-----------|-----------|-----------|-------------------------|
| | | 1977–1981 | 1982–1986 | 1987–1991 | 1977–1991 | |
| 0–29 | 1203 | 0 | 0 | 0 | 0 | 0 |
| 30–34 | 3194 | 0 | 0 | 1 | 1 | 0 |
| 35–39 | 4846 | 1 | 4 | 5 | 10 | 5 |
| 40–44 | 5515 | 3 | 7 | 11 | 21 | 12 |
| 45–49 | 4549 | 3 | 5 | 10 | 18 | 12 |
| 50–54 | 1820 | 1 | 6 | 8 | 15 | 10 |
| 55–59 | 457 | 0 | 2 | 1 | 3 | 3 |
| 60–64 | 218 | 1 | 1 | 0 | 2 | 2 |
| ≥ 65 | 333 | 1 | 0 | 0 | 1 | 1 |
| TOTAL | 22,135 | 10 | 25 | 36 | 71 | 45 |

Table 3. Relative risk (RR) of ovarian cancer among women after abdominal hysterectomy (only on benign indication) and among all age matched women without hysterectomy. Nationwide follow up: 12.5 years (1977–1991).

| Hysterectomy | No. with ovarian cancer | Person-years | Incidence rate per 1000 person-years | Extrapolated lifetime risk of ovarian cancer (%) | RR (95% CI) |
|--------------|-------------------------|--------------|--------------------------------------|--|------------------|
| No | 10,659 | 31,421,934 | 0.34 | 2.7 | 1.0 |
| Yes | 71 | 267,913 | 0.27 | 2.1 | 0.78 (0.60–0.96) |

years, the estimated cumulative lifetime risk of developing ovarian cancer before the age of 80 years among women who had undergone hysterectomy was 2.1%.

In the general population the corrected incidence of ovarian cancer for the period 1977 to 1991 was estimated to 0.34 per 1000 person-years. Assuming an unchanged incidence rate in the future, the lifetime risk of developing cancer before the age of 80 years was estimated to be 2.7%. The relative risk of ovarian cancer among women who had undergone hysterectomy compared with the risk among those who had not was 0.78 (95% CI 0.60–0.96).

DISCUSSION

Evaluation of results

The primary advantages of this register study is the nationwide complete data, the historical prospective design, the relatively long follow up period of 12.5 years and the application of a control group from the same population.

On the other hand, a study based on data from registers does not permit detailed confounder adjustments according to other risk factors (use of oral contraceptives, parity, age at first delivery, breastfeeding, family history of ovarian cancer, etc)^{8–12} except age. We have not, however, any reason to believe that these potential confounders should differ materially between the group of women with hysterectomy and women

without hysterectomy. Adjustment for some risk factors of ovarian cancer in previously conducted case-control^{8,9,11,13} and the prospective study¹⁶ did not appreciably change the risk estimates.

Our study population had one or two ovaries retained. Some previous studies have demonstrated no difference in risk between women who underwent hysterectomy alone *versus* hysterectomy with unilateral oophorectomy^{11,13,14}. The fact that few women without oophorectomy during the study period may previously have had a unilateral oophorectomy therefore hardly have influenced the results substantially.

The estimated lifetime risk of ovarian cancer after hysterectomy (2.1%) is a minimum-estimate since the incidence rate in our study increased during the observation period. As the incidence rate of ovarian cancer after hysterectomy in the last five years of the follow up period was 0.33 per 1000 women-years, compared with 0.34 per 1000 women-years among women who had not undergone hysterectomy, the cumulated risk of ovarian cancer among women who have undergone hysterectomy with time probably approach the risk among women who have not undergone hysterectomy.

Comparison with other studies

Several previously conducted case-control studies have demonstrated odds ratios of ovarian cancer of 0.5 to 0.7 among women who had compared with controls who had not undergone hysterectomy^{7–14}. A prospective

cohort study of 11,017 women who had and 110,683 women who had not undergone hysterectomy demonstrated a relative risk of ovarian cancer of 0.67 (95% CI 0.45–1.00)¹⁶. Thus, women who have undergone hysterectomy consistently have a decreased risk of ovarian cancer after hysterectomy. Our study suggests that the relative protection fades out with time, which could be explained by the healthy screenee effect. Meanwhile, other studies have demonstrated that the reduced risk of developing ovarian cancer after hysterectomy endured longer than 15 to 20 years^{9,11–13,16}. We intend to follow the cohort of hysterectomised women in order to see whether this protection disappears after 15 to 20 years.

Several mechanisms have been suggested to explain the reduced incidence of ovarian cancer after hysterectomy. The healthy screenee effect may be the major explanation in the first years after hysterectomy¹⁴. Biological effects, such as altered ovarian blood flow¹¹, a reduced number of ovulations after hysterectomy¹² or prevented ovarian exposure to carcinogens (talc, infection/virus, menstrual debris with retrograde menstruation) from the perineum, vagina or uterine cavity after hysterectomy may also have an influence²¹. Finally, it has been suggested that the condition which necessitated a hysterectomy is somehow associated with a relatively low risk of ovarian cancer¹⁴.

Prophylactic oophorectomy

Literature reviews^{1,22} have demonstrated that prophylactic oophorectomy from the age of 40 years may prevent 5% to 9% of all ovarian cancer cases. However, the elevated risk of cardiovascular diseases and osteoporosis among women not having hormone replacement therapy will counterbalance this benefit^{23,24}. On the other hand, the reduced risk of ovarian cancer after hysterectomy without oophorectomy might lead to a more conservative attitude concerning prophylactic oophorectomy. A review of the function of the ovaries after premenopausal hysterectomy²⁵ concluded that well designed studies are lacking but that several, mainly older retrospective and uncontrolled studies have demonstrated earlier menopause and an increased incidence of climacteric symptoms²⁶ and benign ovarian cysts (residual ovarian syndrome after hysterectomy^{27–29}). Premenopausal hysterectomy may cause histological changes in the ovaries³⁰, and some studies have demonstrated a transient decrease in oestrogen and progesterone levels³¹. The majority of studies, however, find no persistent changes in the level of hormones^{28,30,32,33}. Whether premenopausal hysterectomy with conservation of at least one ovary is combined with an increased risk of cardiovascular disease^{34–37} and osteoporosis³⁸, still remains an unsolved issue.

The role of ovaries among postmenopausal women has also to be taken into account. Low doses of oestrogen are produced several years after the menopause and testosterone is produced in the ovaries throughout life. Androgens seem to have a positive effect on the sexual function³⁹ and may influence the quality of life, but possibly also have a negative effect caused by an increased risk of cardiovascular diseases^{40,41}.

With a 20% frequency of hysterectomies, the per-operative screening of ovaries may have a small but significant health impact on the incidence of ovarian cancer. Besides all the benefits of the new alternatives to hysterectomy (endometrial ablation, progesterone intrauterine devices and thermal destruction of the endometrium), these alternative approaches imply the lack of visualisation of the ovaries. If one half of the women who have previously undergone hysterectomy are treated in the future by these alternative techniques, we should expect an increase in the incidence of ovarian cancer of a few percent.

We advocate for an individual attitude concerning oophorectomy at hysterectomy. Every case demands a weighing of the risk of developing diseases in the ovary against the benefits of continued ovarian function, although the function in some cases may be reduced. Factors such as age, family history of ovarian cancer, indication for operation and surgical approach, possible contraindications and compliance to hormone replacement therapy together with the wish of the patient have to be considered before the decision.

CONCLUSION

Besides the treatment of the disease indicating a hysterectomy, women preserving at least one ovary have a significantly decreased risk of ovarian cancer for at least 10 years after the operation compared with women without hysterectomy. In this study the reduced risk diminished with time and seems to be a consequence primarily of removal of suspicious ovaries at hysterectomy.

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