

# Tubal sterilization and risk of ovarian, endometrial and cervical cancer. A Danish population-based follow-up study of more than 65 000 sterilized women

Susanne K Kjaer,<sup>1</sup> Lene Mellemkjaer,<sup>1</sup> Louise A Brinton,<sup>2</sup> Christoffer Johansen,<sup>1</sup> Gloria Gridley<sup>2</sup> and Jørgen H Olsen<sup>1</sup>

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**Background** On the basis of a population-based cohort, we assessed the cancer risk, focusing on gynaecological cancers and pre-malignant lesions, among women with a previous tubal sterilization.

**Methods** Using the Danish Hospital Discharge Register we identified 65 232 women who had a tubal sterilization (1977–1993). The cohort was followed for cancer occurrence, and compared with the expected number based on the national cancer incidence rates.

**Results** The overall risk of ovarian cancer was decreased (standardized incidence ratio [SIR] = 0.82; 95% CI: 0.6, 1.0), and it was still decreased  $\geq 10$  years after the sterilization (SIR = 0.65; 95% CI: 0.4, 1.0). The rate of endometrial cancer was also decreased (SIR = 0.66; 95% CI: 0.5, 1.0), the risk continued being moderately reduced during follow-up, although it was not statistically significant.

**Conclusions** In this nationwide, population-based study we find that women with tubal sterilization have a decreased risk of subsequent development of ovarian cancer. As the protective effect is not decreasing with years of follow-up, our data do not support that 'screening' bias can explain the protective effect, but indicate that the sterilization itself may convey a reduction in risk. The same pattern is found for endometrial cancer, the association being less strong.

**Keywords** Tubal sterilization, cohort study, risk, gynaecological cancer

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A history of tubal sterilization has been associated, in some studies, with a reduced risk of ovarian cancer.<sup>1–7</sup> In at least two other studies, however, no such association was seen.<sup>8,9</sup> In addition, there has been little consensus with regard to ovarian cancer risk in relation to years of follow-up.

Only a few studies have reported on the risk of other types of cancer. In one case-control study the risk of endometrial cancer was moderately, but non-significantly, decreased,<sup>10</sup> while two other case-control studies showed a non-significantly increased

risk for this cancer type.<sup>11,12</sup> In yet another study, a small, non-significant reduction of invasive cervical cancer was reported, particularly during the first 5–10 years following the tubal sterilization.<sup>13</sup>

In relation to both ovarian cancer and endometrial and breast cancer, it has been hypothesized that the decreased risk, if confirmed, could be related to alterations in the levels of endogenous hormones (oestrogen, progesterone), which may occur following tubal sterilization.<sup>14–16</sup> A possibly decreased risk of cervical cancer has been related to a screening effect as tubal ligation may provide an opportunity for Pap smear screening and thereby secondary prevention of cervical cancer.<sup>13</sup>

The purpose of the present study was to examine the risk of gynaecological cancer in a cohort of more than 65 000 Danish women who had a tubal sterilization performed during 1977–1993. In addition, we report on the risk of ovarian borderline tumours and cervical intraepithelial neoplasia grade 3

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<sup>1</sup> Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark.

<sup>2</sup> Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA.

Correspondence: Susanne K Kjaer, Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100, Copenhagen Ø, Denmark. E-mail: susanne@cancer.dk

(CIN3), which to our knowledge has not previously been evaluated in follow-up studies.

## Methods

The population-based Danish Hospital Discharge Register (HDR) keeps a record of virtually all (~99%) the somatic hospitalizations in Denmark since 1977.<sup>17</sup> This computerized, central register contains, for each discharge, information on the personal identification number of the patient, dates of admission/discharge, up to 20 diagnoses, and every surgical procedure performed during the respective admission. The surgical procedures are recorded and classified according to The Danish Classification of Surgical Procedures and Therapies.<sup>18</sup> There were 65 366 women ( $\leq 45$  years) who underwent tubal sterilization (operation codes: 60800 60810 60820 60830 60840) in the time period 1977–1993. On these women we also collected information on hysterectomy (operation codes: 61000 61020 61040) and bilateral oophorectomy (operation codes: 60120, 60320).

Since 1968, all Danish inhabitants have been assigned a unique personal identification number, comprising information on sex and date of birth, and these identification numbers are registered in the computerized Central Population Register. The number allows correct linkage of information between different registers. The study cohort was linked to the Central Population Register to verify the personal identification number and to obtain information on date of death or date of migration, when-ever appropriate. A total of 134 women (0.2%) were excluded because of invalid personal identification number.

To ascertain the cancer occurrence in the cohort, it was linked to the Danish Cancer Registry, which contains information on all cases of cancer in Denmark since 1943, including bladder papillomas and benign brain tumours. With regard to the cervical precancerous lesions, carcinoma *in situ* and severe dysplasia (CIN 3) may be close to complete registration, the notification of moderate and mild dysplasia is incomplete.<sup>19</sup> Since 1987, it has been mandatory to report cancer cases as well as precancerous lesions to the Danish Cancer Registry. The cancers are classified according to a modified version of the Seventh Revision of the International Classification of Diseases (ICD).<sup>19</sup>

The 65 232 women were followed for cancer occurrence (including borderline ovarian tumours and CIN3) from the date of the hospital discharge for tubal sterilization until the date of emigration, date of death, or 31 December 1995, whichever came first. Additional exit dates were applied when the risk of certain cancers was examined. Thus, follow-up for endometrial cancer was ended at the date of hysterectomy, follow-up for cervical cancer/CIN3 was discontinued at the date of total hysterectomy, and follow-up for ovarian cancer/borderline tumour was ended at the date of bilateral oophorectomy.

The observed number of cancer cases was compared with the number of expected cases based on the age- and calendar year-specific cancer incidence rates for women from the Danish Cancer Registry and accumulated person-years. Standardized incidence ratios (SIR) (observed number of cases divided by the expected number) were computed with corresponding 95% CI for each type of cancer, assuming a Poisson distribution of the observed cancer cases.<sup>20</sup>

## Results

The study cohort of 65 232 sterilized women accrued 643 761 person-years during follow-up. The mean follow-up time was 9.9 years (range:  $>0$ –19 years). Less than 2% of the women were  $\leq 24$  years at the time of sterilization, while 15% were 25–29 years, 30% were 30–34 years, 35% 35–39 years, and about 18% were 40–45 years when they had their tubal sterilization. In the follow-up for ovarian cancer/borderline tumours, endometrial cancer and invasive cervical cancer/CIN3, respectively, 641 702, 604 248, and 605 631 person-years were accrued. Thus, censoring the observation time subsequent to bilateral oophorectomy, hysterectomy, and total hysterectomy reduced the total number of person-years by 0.3%, 6.1%, and 5.9%, respectively. For 99.1% of the women, the type of tubal sterilization was only registered as laparoscopic sterilization without further specification.

A total of 1894 cancers were observed among the 65 232 women who previously had a tubal sterilization. This was slightly less than expected (1981 cases) on the basis of the rates from the general female population (SIR = 0.96; 95% CI: 0.9, 1.00) (Table 1). None of the non-gynaecological cancers contributed in particular to this lower overall cancer rate, except for breast cancer, which occurred less frequently than expected (SIR = 0.9; 95% CI: 0.9, 1.0). In contrast, the group of gynaecological cancers played a role as a total of 277 cases was observed in this population against 328.0 expected (SIR = 0.84; 95% CI: 0.8, 1.0).

In Tables 2 and 3, the SIR are presented for specific types of gynaecological cancers as well as for the ovarian borderline tumours and CIN3. The overall risk of ovarian cancer was decreased (SIR = 0.82), although the association only reached borderline statistical significance (95% CI: 0.6, 1.0). However, when considering the groups with long-term follow-up, there was still a pattern of a decreased risk. Ten years or longer after the sterilization the SIR was 0.65 (95% CI: 0.4, 1.0) (Table 2), and even in women followed for  $\geq 15$  years after the tubal sterilization, the risk tended to be reduced, although this was not statistically significant (SIR = 0.65; 95% CI: 0.2, 1.4) (data not shown). We also looked at the risk of ovarian cancer in relation to age at sterilization. We observed the same decreased ovarian cancer risk in women  $< 35$  years of age at time of sterilization (SIR = 0.78; 95% CI: 0.5, 1.2) as in women who were  $\geq 35$  years (SIR = 0.83; 95% CI: 0.6, 1.1) (data not shown).

A total of 21 ovarian borderline tumours were observed in this cohort, yielding a non-significantly decreased risk (SIR = 0.82; 95% CI: 0.5, 1.3). The risk estimates did not change much with years of follow-up after the sterilization (Table 2).

The risk of ovarian cancer of different histological types (serous, mucinous, clear cell/endometrioid, others) was also assessed (Table 2). For both the group of serous invasive tumours as well as for the group of 'other' ovarian cancers, the overall risk was decreased; SIR = 0.72 (95% CI: 0.5, 1.0) and SIR = 0.60 (95% CI: 0.3, 1.0), respectively. In addition, the clear cell/endometrioid group was non-significantly decreased (SIR = 0.86; 95% CI: 0.5, 1.44). In contrast, the mucinous ovarian cancers were more common than expected, SIR = 1.49 (95% CI: 0.9, 2.3). For women with  $\geq 5$  years of follow-up, this risk of mucinous ovarian carcinoma increased to 1.86 (95% CI: 1.1, 3.0)

**Table 1** Standardized incidence ratios (SIR) for gynaecological cancer and specified groups of non-gynaecological cancer following tubal sterilization among 65 232 Danish women

Cancer site	Observed	Expected	SIR	95% CI
All malignant neoplasms	1894	1980.7	0.96	(0.9, 1.0)
Gynaecological cancers	277	328.0	0.84	(0.8, 1.0)
Non-gynaecological cancers	1617	1652.7	0.98	(0.9, 1.0)
Buccal cavity and pharynx	17	19.5	0.87	(0.5, 1.4)
Digestive organs	134	146.8	0.91	(0.8, 1.1)
Lung	89	99.0	0.90	(0.7, 1.1)
Breast	630	988.4	0.92	(0.9, 1.0)
Urinary system	45	41.2	1.09	(0.8, 1.5)
Melanoma of the skin	143	129.1	1.11	(0.9, 1.3)
Other skin	301	286.6	1.05	(0.9, 1.2)
Brain and nervous system	81	82.7	0.98	(0.8, 1.2)
Thyroid	26	21.5	1.21	(0.8, 1.8)
Lymphatic and haematopoietic	96	81.0	1.18	(1.0, 1.5)
Other specified	24	25.0	0.96	(0.8, 1.8)
Secondary and unspecified	30	31.1	0.97	(0.7, 1.4)

**Table 2** Standardized incidence ratios (SIR) for ovarian cancer and borderline ovarian tumour by length of follow-up after tubal sterilization

Years since sterilization	Ovarian cancer				Borderline ovarian tumour			
	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95% CI
<b>All histological types</b>								
<1		4.7	0.43	(0.1, 1.6)	1.5	—	—	—
1–4	17	24.0	0.71	(0.4, 1.1)	7.5	0.94	0.94	(0.4, 1.9)
5–9	37	34.1	1.08	(0.8, 1.5)	9.5	0.84	0.84	(0.4, 1.7)
>10	19	29.1	0.65	(0.4, 1.0)	7.0	0.86	0.86	(0.3, 1.9)
Total	75	91.8	0.82	(0.6, 1.0)	25.5	0.82	0.82	(0.5, 1.3)
<b>Serous type</b>								
<4	9	11.3	0.80	(0.4, 1.5)				
>5	17	24.9	0.68	(0.4, 1.1)				
Total	26	34.2	0.72	(0.5, 1.1)				
<b>Mucinous type</b>								
<4	3	4.1	0.73	(0.2, 2.1)				
>5	16	8.6	1.86	(1.1, 3.0)				
Total	19	12.8	1.49	(0.9, 2.3)				
<b>Clear cell/endometrioid type</b>								
<4	1	4.6	0.22	(0.0, 1.2)				
>5	13	11.7	1.11	(0.6, 1.9)				
Total	14	16.3	0.86	(0.5, 1.4)				
<b>Other types</b>								
<4	6	8.6	0.70	(0.3, 1.5)				
>5	10	18.0	0.56	(0.3, 1.0)				
Total	16	26.6	0.60	(0.3, 1.0)				

The rate of endometrial cancer was also decreased in women who had a tubal sterilization (SIR = 0.70; 95% CI: 0.5, 1.0) and except for the first year after the operation. The risk continued being moderately reduced during follow-up, however the associations were not statistically significant (Table 3).

The observed number of cervical cancer cases was only slightly lower than expected, both overall and during follow-up, except for the first year where a non-significantly increased risk was observed (Table 3). In contrast, CIN3 lesions were slightly in excess (SIR = 1.06; 95% CI: 1.0, 1.1), the risk being significantly

**Table 3** Standardized incidence ratios (SIR) for endometrial and cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3) by length of follow-up after tubal sterilization

Years since sterilization	Endometrial cancer				Cervical cancer				CIN3			
	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95%CI	Obs.	Exp.	SIR	95% CI
<1		1.6	1.29	(0.1, 4.7)		15.7	1.21	(0.7, 1.9)		122.2	1.70	(1.5, 2.0)
1–4	4	9.0	0.44	(0.1, 1.1)	62	63.7	0.97	(0.8, 1.3)	362	417.3	0.87	(0.8, 1.0)
5–9		15.8	0.70	(0.4, 1.2)	48	56.9	0.84	(0.6, 1.1)	284	279.4	1.02	(0.9, 1.1)
>10	13	16.3	0.80	(0.4, 1.4)	26	27.7	0.94	(0.6, 1.4)	124	100.7	1.23	(1.0, 1.6)
Total	30	42.7	0.70	(0.5, 1.0)	155	164.1	0.94	(0.8, 1.1)		919.5	1.06	(1.0, 1.1)

**Table 4** Recent studies of the association between tubal sterilization and ovarian cancer

Author	Study design Study period	Size of study. Frequency of exposure	Measures of association	Comments
Rosenblatt <i>et al.</i> , 1996 WHO Collaborative Study	case-control (hospital-based) 1979–1988	385 cases (104 borderline) 2563 controls 34 cases (8.8%) and 426 controls (17.1%) with tubal sterilization	OR <sup>a</sup> adj = 0.71 (0.47, 1.08) No trend with time since tubal sterilization <i>Clear cell:</i> OR = 0.33 (0.007, 2.68) <i>Endometrioid:</i> OR = 0.21 (0.048, 1.49)	Adjusted for: parity and OC <sup>b</sup> use, Contraceptive use. Estimates based on 1 exposed case for both clear cell tumours and for Endometrioid tumours
Cornelison <i>et al.</i> , 1997 (USA)	case-control (hospital-based) 1982–1988	300 cases 606 controls 26 cases (9%) and 93 controls (15.5%) with tubal sterilization	ORadj = 0.52 (0.31, 0.85) For 5–20 years after tubal Sterilization, risk tended to be more decreased than for >21 years	Adjusted for: socioeconomic level, marital status, parity, age at first pregnancy, Menarche, menopause, irregular menses, breast feeding, body habitus, and OC use.
Green <i>et al.</i> , 1997 (Australia)	case-control (controls randomly selected from electoral roll) 1990–1993	824 cases 855 controls 104 cases (13%) and 194 controls (23%) with tubal sterilization	ORadj = 0.61 (0.46, 0.85) Risk was decreased even after >25 years	Adjusted for: age, education, body mass index, parity, duration of OC use, smoking and family history of ovarian cancer.
Miracle- Cohort McMahill <i>et al.</i> , 1997 (USA)	(ovarian cancer mortality) 1982–1991	396 114 women 799 ovarian cancer deaths 24 women (3%) had a tubal sterilization	HR <sup>c</sup> = 0.64 (0.42, 0.96) HRadj = 0.68 (0.45, 1.03) Risk was greater the first 20 years than later	Adjusted for: age at interview, race, body mass index, education, family, history of ovarian/breast cancer, no. of pregnancies, marital status, menarche, menopause, OC use, HRT use, no. of miscarriages, smoking
Krieger <i>et al.</i> , 1997 (Canada)	Cohort (ovarian cancer incidence) 1973–1993	251 907 women having had tubal ligation 108 ovarian cancers	SIR <sup>d</sup> = 0.57, <i>P</i> < 0.001 Risk was decreased even after >10 years	No adjustment for confounding factors

<sup>a</sup> Odds ratio.<sup>b</sup> Oral contraceptive.<sup>c</sup> Hazard ratio.<sup>d</sup> Standardized incidence ratio.

increased within the first year after sterilization and also in the group with the longest follow-up.

## Discussion

In the present study following more than 65 000 women with a tubal sterilization, we find that tubal sterilization is associated with a reduced risk of ovarian cancer. This is in line with both early studies (summarized by Hankinson *et al.*<sup>2</sup> and

Miracle-McMahill *et al.*<sup>6</sup>) and with those most recently published<sup>3–7</sup> (Table 4). It has been suggested that screening of the ovaries during the surgical procedure may be the main reason for the protective effect of sterilization. If true, it should be anticipated that the protective effect would decrease with number of years since the operation. Our results disagree with this hypothesis, as the risk remained decreased even after 10–15 years of follow-up. The results are in line with those of case-control studies showing a protective effect that remained

up to 25 years after sterilization.<sup>5</sup> They are also in agreement with the results of the only other follow-up study assessing ovarian cancer incidence by years since tubal ligation.<sup>7</sup> Finally, a protective effect of the surgical procedure of sterilization itself (rather than a screening effect) may be supported indirectly by the finding of Krieger *et al.*<sup>7</sup> of no protective effect of unilateral ovariectomy, where a similar screening effect could be anticipated.

Several hypotheses have been suggested to establish the biological plausibility and explain a protective effect of tubal sterilization on ovarian cancer risk. The majority of ovarian cancers develop from the cells of the surface epithelium. During each ovulation, these cells are involved in follicular rupture and increased cell division in relation to the subsequent wound repair. Fatallas 'incessant ovulation' hypothesis suggested that these repeated minor traumas to the ovarian surface epithelium increase the risk of ovarian cancer.<sup>21</sup> In line with this, the number of ovulations during lifetime, as well as factors associated with increased/decreased number of ovulations (nulliparity, oral contraceptive [OC] use), have been identified as important risk determinants for cancer of the ovaries.<sup>22,23</sup> Likewise, high levels of circulating gonadotrophins from the pituitary gland have been suggested as playing an important role in ovarian carcinogenesis ('gonadotrophin hypothesis').<sup>24,25</sup> It has been suggested that following sterilization, the ovarian circulation may be impaired<sup>26</sup> causing suppressed ovarian hormone production followed by some degree of anovulation, and thereby maybe a reduction in the risk of ovarian cancer. Furthermore, the levels of circulating hormones may be changed, also affecting the ovarian cancer risk. In addition, it has been hypothesized that because of a reduction in the utero-ovarian circulation, caused by the tubal sterilization, reduced concentrations of uterine growth factors reach the ovaries resulting in decreased ovarian cancer risk.<sup>27</sup> Similarly, the changes in the endogenous hormone level after tubal sterilization may imply a different oestrogen/progesterone ratio and this has been hypothesized to be related to the risk of endometrial cancer.<sup>28,29</sup> However, results from the studies forming the basis for these hypotheses are somewhat conflicting. In some studies, a decreased oestrogen and maybe progesterone level has been observed after tubal sterilization,<sup>16,30,31</sup> whereas in others no changes were found.<sup>32,33</sup> Finally, another theory has suggested that tubal ligation may prevent talc or other carcinogens from ascending the tubes and coming in contact with the ovaries. However, the current conclusion is that the mechanism underlying the apparent protective effect of tubal ligation is still not adequately elucidated.

Rosenblatt *et al.*<sup>3</sup> reported that the effect of tubal ligation was seen only for clear cell and endometrioid ovarian carcinomas. However, the results were based only on one exposed case in each group. This finding could not be confirmed in the present study. In our study, the overall decrease in ovarian cancer risk seemed to affect the non-mucinous histological types only. It has previously been suggested that mucinous ovarian cancers have a different pattern of risk factors from the non-mucinous types.<sup>34</sup> This relates in particular to use of OC and to parity. However, the currently available data on this issue are equivocal. Some studies have found use of OC and increasing parity to decrease the risk of both mucinous and non-mucinous ovarian cancer.<sup>35-37</sup> In contrast, others observed such a decreased risk only for the non-mucinous tumours, whereas for

ovarian cancer of the mucinous type they found no or even an increased risk associated with OC use and parity.<sup>34,38-40</sup> If the development of mucinous ovarian tumours is less dependent on hormonal/ovulatory factors as indicated by some studies,<sup>41</sup> it might be anticipated that a protective effect of sterilization would also be less pronounced for these tumours. Indeed, the results of the present paper may support a different aetiological mechanism for ovarian cancers of the mucinous type, however, due to relatively small numbers when ovarian cancer is divided into histological groups, we cannot exclude the possibility that the findings may be due to chance.

Only a few case-control studies and no follow-up studies have focused on the association between tubal ligation and the risk of endometrial cancer.<sup>10-12,42</sup> In one study, a significantly decreased crude risk was observed; however, after adjustment for confounding factors like age and parity, only a moderately (non-significant) decreased risk remained.<sup>10</sup> In the same study, the reduction in risk tended to diminish with time since the sterilization, maybe pointing to some degree of surveillance effect. In another study, based on results from the World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives, it was concluded that the existing findings with regard to the association between endometrial cancer and previous sterilization could most likely be ascribed to random variation.<sup>11</sup> This is supported by the most recent study in which no significant association was observed between sterilization and endometrial cancer after adjustment for parity was done.<sup>12</sup> In our study, we find an overall decreased risk of endometrial cancer, and we observe no significant tendency that the effect diminishes with length of follow-up. However, as we did not have information on other risk factors, we were unable to make any adjustments for potential confounding factors. Thus, even though it is in theory biologically plausible that sterilization affects endometrial cancer risk, it is still unclear whether a causal association exists.

We find that the occurrence of uterine cervical cancer was slightly lower and the occurrence of CIN3 higher than could be expected from the rates in the general population. Our results for invasive cervical cancer are almost identical to those recently reported by Li *et al.*<sup>13</sup> The association between tubal sterilization and CIN3 has not previously been addressed. The finding of a decrease (although limited) in cancer of the cervix and simultaneously increased detection of CIN3, which is only rarely symptomatic, most likely point to a screening effect i.e. in connection with the surgical procedure, a high proportion of women will also have a Pap smear.

A well-defined study population and a large cohort size strengthen this nationwide, population-based study. Furthermore, information on outcome is nearly complete and there is virtually no loss to follow-up, due to the accuracy and completeness of the Danish Cancer Registry and the Central Population Register. Finally, except for the study by Krieger *et al.*,<sup>7</sup> this is the only study where information on exposure is not dependent on patient recall. It is a limitation of the present study, however, that we had no information on the type of sterilization, and thus were unable to assess whether the cancer risk varied with the different methods of tubal sterilization. In addition, no information on potential confounding factors was available. It is likely that women having a tubal sterilization have more children than other women or at least a lower

prevalence of infertility, and consequently an *a priori* lower risk of ovarian/endometrial cancer. It is also clear that having a tubal ligation, and the age at which this occurs, could influence the total duration of OC use as well as the number of children. Both of these variables constitute important risk determinants for ovarian cancer, and thus our inability to adjust for these factors may well have influenced the results of our study. Nevertheless, it seems less likely that this can account entirely for our findings with regard to ovarian cancer. In none of the recent studies mentioned in Table 4, where information on such factors was collected, neither parity alone nor in combination with other risk determinants could explain the association between tubal sterilization and ovarian cancer (Table 4). Furthermore, if the association could be explained by a reduction in the length of time when a woman could use OC or could have children, one might expect a different magnitude of association in women having their tubal ligation at a young age compared with women sterilized later in life, and we did not observe such a difference (data not shown). Finally, inclusion of women who are actually not at risk (e.g. women with a hysterectomy or bilateral oophorectomy) in the denominator of the standard rate may imply underestimation of the expected number and thus overestimation of the relative rate. As only about 1800 women undergo bilateral oophorectomy and 5500 women have

a hysterectomy each year (out of a population of approximately 1.8 million women aged 15–69 years),<sup>43</sup> the effect on the ovarian cancer SIR estimate is considered limited.

In conclusion, in this nationwide, population-based study we find that women with tubal sterilization have a decreased risk of subsequent development of ovarian cancer, which seems to last for at least 10–15 years, and likewise, a slight reduction in the occurrence of ovarian borderline tumours is observed. Our data do not support that screening bias can explain the protective effect against ovarian cancer, but indicate that the sterilization itself may convey a reduction in risk, although the biological mechanism is not entirely clear. The same overall pattern is found for endometrial cancer; however, the association is weaker than for cancer of the ovaries. In contrast, the moderately decreased cervical cancer risk and increased risk of CIN3 observed in our cohort indicate that the effect of tubal sterilization in this case can be explained by an increased cervical cancer screening among sterilized women.

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### KEY MESSAGES

- Women with a tubal sterilization have a decreased risk of developing ovarian cancer.
- The effect on borderline tumours was less pronounced.
- The protective effect does not seem to diminish significantly with time since the sterilization.
- The decreased risk did not apply to the group of mucinous ovarian cancers, and thus our data may support the previously suggested hypothesis of a different aetiological mechanism for this histological type.
- A decreased risk of endometrial cancer following tubal sterilization was observed, although the association seemed less strong than for ovarian cancer.
- A slightly decreased risk of cervical cancer together with an increased risk of cervical intraepithelial neoplasia grade 3 (CIN3) point to increased cervical cancer screening activity among sterilized women.

## References

- Whittemore AS, Harris R, Itnyre J *et al.* Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancer in white women. *Am J Epidemiol* 1992;**136**:1184–203.
- Hankinson SE, Hunter DJ, Colditz GA *et al.* Tubal ligation, hysterectomy and risk of ovarian cancer. *JAMA* 1993;**270**:2813–18.
- Rosenblatt KA, Thomas DB and The World Health Organization Collaborative Study of Neoplasia and Steroid Contraception (1996). Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. *Cancer Epidemiol Biomark Prev* 1996;**5**:933–35.
- Cornelison TL, Natarajan N, Piver MS, Mettlin CJ. Tubal ligation and the risk of ovarian carcinoma. *Cancer Detect Prev* 1997;**21**:1–6.
- Green A, Purdie D, Bain C *et al.* Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. *Int J Cancer* 1997;**71**:948–51.
- Miracle-McMahill HL, Calle EE, Kosinski AS *et al.* Tubal ligation and fatal ovarian cancer in a large prospective study. *Am J Epidemiol* 1997;**145**:349–57.
- Krieger N, Sloan M, Cotterchio M, Parsons P. Surgical procedures associated with risk of ovarian cancer. *Int J Epidemiol* 1997;**26**:710–15.
- McGowan L, Parent L, Lednar W *et al.* The woman at risk for developing ovarian cancer. *Gynecol Oncol* 1979;**7**:325–44.
- Koch M, Starreveld AA, Hill GB *et al.* The effect of tubal ligation on the incidence of epithelial cancer of the ovary. *Cancer Detect Prev* 1984;**7**:241–45.
- Castelsagué X, Thompson WD, Dubrow R. Tubal sterilization and the risk of endometrial cancer. *Int J Cancer* 1996;**65**:607–12.
- Rosenblatt K, Thomas D. Association between tubal ligation and endometrial cancer. *Int J Cancer* 1997;**71**:129–30.

- <sup>12</sup> Lacey JV, Brinton LA, Mortel R *et al.* Tubal sterilization and the risk of cancer of the endometrium. *Gynecol Oncol* 2001;**79**:482–84.
- <sup>13</sup> Li H, Thomas DB. Tubal ligation and risk of cervical cancer. *Contraception* 2000;**61**:323–28.
- <sup>14</sup> Sørensen T, Ladehoff P, Lindholm P, Quist K. Follicular stimulating hormone, luteinizing hormone and estrogen levels before and after female sterilization. *Acta Obstet Gynecol Scand* 1981;**50**:559–61.
- <sup>15</sup> Cattanach JF, Milne BJ. Post-tubal ovulatory problems correlated with ovarian steroidogenesis. *Contraception* 1988;**38**:541–50.
- <sup>16</sup> Hakverdi AU, Taner CE, Esden AC, Satici O. Changes in ovarian function after sterilization. *Adv Contracept* 1994;**10**:51–56.
- <sup>17</sup> Danish National Board of Health. *Activity in the Hospital Care System 1979*. Copenhagen: Danish National Board of Health, 1981.
- <sup>18</sup> Danish National Board of Health. *Classification of Surgical Procedures and Therapies. 1st, 2nd and 3rd Edns*. Copenhagen: Danish National Board of Health 1973, 1980, 1988.
- <sup>19</sup> Storm HH, Mandres T, Friis S, Bang S. *Cancer Incidence in Denmark in 1988*. Copenhagen: Danish Cancer Society, 1991.
- <sup>20</sup> Bailar JC, Ederer F. Significance factors for the ratio of a Poisson variable to its expectation. *Biometrics* 1964;**20**:639–43.
- <sup>21</sup> Fatalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet* 1971;**ii**:163.
- <sup>22</sup> Purdie D, Green A, Bain C *et al.* Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. *Int J Cancer* 1995;**62**:678–84.
- <sup>23</sup> Risch HA, Marrett LD, Howe GR. Parity, contraception, infertility and the risk of epithelial ovarian cancer. *Am J Epidemiol* 1994;**140**:585–97.
- <sup>24</sup> Stadel BV. The etiology and prevention of ovarian cancer. *Am J Obstet Gynecol* 1975;**123**:772–74.
- <sup>25</sup> Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *J Natl Cancer Inst* 1983;**71**:717–21.
- <sup>26</sup> Rilman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiologic evidence. *Clin Endocrinol* 1998;**49**:665–70.
- <sup>27</sup> Cramer DW, Xu H. Epidemiologic evidence for growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol* 1995;**5**:310–14.
- <sup>28</sup> Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. *Cancer Res* 1982;**42**:3232–39.
- <sup>29</sup> Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis* 2000;**21**:427–33.
- <sup>30</sup> Radwanska E, Headley SK, Dmowski P. Evaluation of ovarian function after tubal sterilization. *J Reprod Med* 1982;**27**:376–84.
- <sup>31</sup> Cattanach JF. Oestrogen deficiency after tubal ligation. *Lancet* 1985;**i**:847–49.
- <sup>32</sup> Garza-Flores J, Vázquez-Estrada L, Reyes A *et al.* Assessment of luteal function after surgical tubal sterilization. *Adv Contracept* 1991;**7**:371–77.
- <sup>33</sup> Erruo W, Bilian X, Weigian Y, Hui L, Beisheng I. Hormonal profile of the menstrual cycle in Chinese women after tubal sterilization. *Contraception* 1992;**45**:583–93.
- <sup>34</sup> Risch AR, Marret LD, Howe JM. Differences in risk factors for epithelial ovarian cancer by histology. *Am J Epidemiol* 1996;**144**:363–72.
- <sup>35</sup> Wittenberg L, Cook LS, Rossing MA, Weiss NS. Reproductive risk factors for mucinous and non-mucinous epithelial ovarian cancer. *Epidemiology* 1999;**10**:761–63.
- <sup>36</sup> Weis NS, Lyon JL, Liff JM, Vollmer WM, Daling JR. Incidence of ovarian cancer in relation to the use of oral contraceptives. *Int J Cancer* 1981;**28**:669–71.
- <sup>37</sup> Cramer DW, Hutchison GB, Welch WR, Scully RE, Ryan RE. Determinants of ovarian cancer risk. I. Reproductive experience and family history. *J Natl Cancer Inst* 1982;**71**:711–16.
- <sup>38</sup> Kvåle G, Heuch I, Nilsen S, Beral V. Reproductive factors and risk of ovarian cancer: a prospective study. *Int J Cancer* 1988;**42**:246–51.
- <sup>39</sup> World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Epithelial ovarian cancer and combined oral contraceptives. *Int J Epidemiol* 1989;**18**:538–45.
- <sup>40</sup> Cramer DW, Hutchison GB, Welch WR, Beral V. Factors affecting the association of oral contraceptives and ovarian cancer. *N Engl J Med* 1982;**307**:1047–51.
- <sup>41</sup> Purdie DM, Siskind V, Bain CJ, Webb PM, Green A. Reproduction-related risk factors for mucinous and nonmucinous epithelial ovarian cancer. *Am J Epidemiol* 2001;**153**:860–64.
- <sup>42</sup> Kelsey JL, Livolsi VA, Holford TR *et al.* A case-control study of the endometrium. *Am J Epidemiol* 1982;**116**:333–42.
- <sup>43</sup> Danish National Board of Health. *Surgical Activity in Danish Hospitals 1992*. Copenhagen: Danish National Board of Health, 1992.