

## Long term effects of hysterectomy on mortality: nested cohort study

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### Abstract

**Objectives** To investigate the long term risk (mean > 20 years) of death from all causes, cardiovascular disease, and cancer in women who had or had not had a hysterectomy.

**Design** Nested cohort study.

**Setting** Royal College of General Practitioners' oral contraception study.

**Participants** 7410 women (3705 flagged at the NHS central registries for cancer and death who had a hysterectomy during the oral contraception study and 3705 who were flagged but did not have the operation).

**Main outcome measures** Mortality from all causes, cardiovascular disease, and cancer.

**Results** 623 (8.4%) women had died by the end of follow-up (308 in the hysterectomy group and 315 in the non-hysterectomy group). Older women who had had a hysterectomy had a 6% reduced risk of death compared with women of a similar age who did not have the operation (adjusted hazard ratio 0.94, 95% confidence interval 0.75 to 1.18). Compared with young women who did not have a hysterectomy those who were younger at hysterectomy had an adjusted hazard ratio for all cause mortality of 0.82 (95% confidence interval 0.65 to 1.03). Hysterectomy was not associated with a significantly altered risk of mortality from cardiovascular disease or cancer regardless of age.

**Conclusion** Hysterectomy did not increase the risk of death in the medium to long term.

### Introduction

Around 20% of women in the United Kingdom have a hysterectomy by age 55.<sup>1</sup> Any long term effects of hysterectomy are therefore important, particularly on all cause mortality and on cardiovascular disease and cancer, the most common causes of death.

The only study to date to examine all cause mortality found no evidence of an association with hysterectomy. But the study may have misclassified hysterectomy status, and follow up was short (5.6 years).<sup>2</sup>

Studies of cardiovascular sequelae have produced conflicting evidence. One study found an increased risk of non-genital (mainly rectal and thyroid) cancer among women after hysterectomy compared with

those with an intact uterus, although the authors concluded hysterectomy was not associated with a substantial effect on cancers in general.<sup>3</sup> Several studies have found a reduced risk of ovarian cancer after hysterectomy without bilateral oophorectomy<sup>4,5</sup> and a decreased risk of breast cancer after hysterectomy (with or without oophorectomy).<sup>6,7</sup> Conversely, a study found that renal cell carcinoma was significantly more common among women who had had a hysterectomy compared with women who had not.<sup>8</sup>

Using data from the Royal College of General Practitioners' oral contraception study, we examined the long term risk of hysterectomy on mortality.

### Methods

#### The oral contraception study

During a 14 month period starting in May 1968, 1400 general practitioners throughout the United Kingdom recruited 23 000 women who were using oral contraceptives, and a similar number of age matched women who had never done so.<sup>9</sup> Baseline information collected included details of any previous use of oral contraceptives, social class,<sup>10</sup> smoking, parity, and important medical history. Every six months the doctors provided updates.

During the mid-1970s, 75% of the cohort was flagged at the NHS central registries for future deaths or cancer registrations. The doctors stopped their observations in 1996, but the study continues to be notified of deaths and cancer registrations.

#### Nested cohort

We identified 3706 women with an intact uterus at recruitment to the oral contraception study who were flagged at the NHS central registries and who subsequently had a hysterectomy during the oral contraception study. These women constituted the exposed group. From the remaining 31 481 non-exposed women, we randomly identified for each woman who had a hysterectomy a woman who was born within one year of the exposed woman, had a different recruiting doctor, and was in the oral contraception study at the time of operation. Each non-exposed woman was assigned a false date for operation



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(pseudo-operation) of the same month and year as the hysterectomy carried out on her matched woman.

For the newly assembled cohort we extracted data on social class and cigarette consumption at recruitment, parity, use of oral contraceptives and hormone replacement therapy, history of uterine fibroma (international classification of diseases, eighth revision),<sup>11</sup> gynaecological malignancy, other malignancy, cardiovascular disease, and hypertension. These data were all up to and including the date of operation or pseudo-operation, except for use of hormone replacement therapy, which was up to the month before the operation or pseudo-operation. When appropriate we also extracted information on the date and cause of death. Follow-up was to 31 December 2003.

### Statistical analysis

We analysed the data using SPSS version 11.5.1. When appropriate we transformed continuous variables into categorical variables. Social class was categorised as non-manual, manual, or other. We compared differences in characteristics between the groups using the  $\chi^2$  test for categorical variables, independent two sample *t* tests for continuous normally distributed variables, and Mann-Whitney tests for non-normally distributed variables.

For each group we generated Kaplan-Meier survival curves comparing the probability of survival from any cause, cardiovascular disease, or cancer to end of follow-up. We applied the log rank test. We examined survival curves for each of the potential confounding variables and survival time, for deviation from the proportional hazards assumption.

We carried out separate analyses for those aged below or equal to the median age at hysterectomy and those aged above, as age at operation may alter the effect of hysterectomy on outcome.

We then used forward conditional stepwise Cox regression to examine the relation between hysterectomy and survival time after adjustment for potential confounding. Into the initial model we entered social class, smoking, age, parity, use of oral contraceptives and hormone replacement therapy, history of malignancy, uterine fibroma, hypertension, or cardiovascular disease, and we retained variables in a stepwise manner if they had a *P* value of  $\leq 0.05$ .

## Results

We excluded one woman and her matched non-exposed comparator owing to lack of information on death from a Mullerian tumour, leaving 7410 women for analysis.

Hysterectomy not elsewhere classified was the most common type of hysterectomy recorded (2526 women, 68.2%). Both groups had similar characteristics at baseline (see *bmj.com*). The median age at time of operation was 43.7 years (interquartile range 38.9-48.1 years). The hysterectomy group had a significantly higher mean parity than that of the non-hysterectomy group (2.55 (SD 1.3) versus 2.47 (SD 1.3) births, *P* = 0.01).

Both groups were followed up for a mean length of 250.3 (SD 87.1) months. By the end of follow-up, 623 (8.4%) women had died; 233 from cancer, 160 from cardiovascular disease, and 230 from other causes.

We found no significant differences between groups in the Kaplan-Meier plots for survival from all cause mortality and mortality due to cardiovascular disease or cancer (plots not shown). We found no obvious deviations from the proportional hazards assumption in the Kaplan-Meier plots for each potential confounding factor. For each of our outcomes, we present hazard ratios only for variables identified important for the final model.

After stepwise adjustment, women who were younger at hysterectomy had a non-significant 18% reduction in their risk of all cause mortality compared with young women not having a hysterectomy (table). Smoking and a history of hypertension or non-gynaecological cancer were each independently associated with all cause mortality in younger women. Women who were older when they had a hysterectomy had an adjusted 6% reduced risk of all cause mortality, compared with older women not having the procedure. In older women, smoking and a history of hypertension, cardiovascular disease, gynaecological cancer, or non-gynaecological cancer was independently associated with death from any cause. All cause mortality was significantly reduced among older women who had used oral contraceptives.

Hysterectomy was not associated with a significantly altered risk of mortality due to cardiovascular disease regardless of age (see *bmj.com*). Smoking and a history of cardiovascular disease or non-gynaecological cancer among younger women was associated with future death from cardiovascular disease. Among older women, smoking and a history of hypertension or cardiovascular disease was associated with an increased risk of death from cardiovascular disease. The risk of death from cardiovascular disease was 40% lower among older women who had ever used oral contraceptives compared with never users (adjusted hazard ratio 0.60, 95% confidence interval 0.39 to 0.92).

Women who were younger at operation had a non-significant reduced risk of death from cancer than similarly aged women who did not have a hysterectomy (adjusted hazard ratio 0.81, 95% confidence interval 0.55 to 1.19; see *bmj.com*). A history of non-gynaecological cancer, however, was associated with a significantly increased risk of death from cancer. In contrast, women who were older when they had their hysterectomy had almost the same risk of death from cancer as similarly aged women not having the procedure (adjusted hazard ratio 1.02, 95% confidence interval 0.69 to 1.49). In the older group, death from cancer was significantly more likely among women who smoked or had a history of gynaecological or non-gynaecological cancer, and was lower in previous users of oral contraception.

## Discussion

In this study, hysterectomy is not associated with an increased long term risk of death from any cause, cardiovascular disease, or cancer.

Information on hysterectomy and potential confounding variables was provided prospectively by doctors participating in the oral contraception study. Information bias would therefore have occurred if they reported information differently on the basis of a woman's hysterectomy status. Such bias is, however, unlikely

Factors associated with all cause mortality in women who had or had not had hysterectomy in relation to median age\*

Characteristic	Women aged ≤43.7 years		Women aged >43.7 years	
	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Hysterectomy:				
No	1.00	1.00	1.00	1.00
Yes	0.88 (0.70 to 1.11)	0.82 (0.65 to 1.03)	0.98 (0.84 to 1.15)	0.94 (0.75 to 1.18)
No of cigarettes per day at recruitment:				
0	1.00	1.00	1.00	1.00
1-14	1.67 (1.24 to 2.25)	1.62 (1.20 to 2.18)	1.60 (1.25 to 2.06)	1.57 (1.22 to 2.03)
≥15	3.16 (2.41 to 4.15)	3.06 (2.33 to 4.02)	2.30 (1.77 to 3.00)	2.24 (1.71 to 2.92)
Oral contraceptive use:				
Never	—	—	1.00	1.00
Ever	—	—	0.78 (0.63 to 0.96)	0.71 (0.57 to 0.88)
History of hypertension:				
No	1.00	1.00	1.00	1.00
Yes	1.87 (1.27 to 2.77)	1.92 (1.30 to 2.84)	1.55 (1.19 to 2.02)	1.67 (1.28 to 2.20)
No of cardiovascular morbidities:				
0	—	—	1.00	1.00
1	—	—	1.48 (0.99 to 2.21)	1.32 (0.88 to 1.98)
≥2	—	—	3.90 (2.28 to 6.65)	2.78 (1.61 to 4.79)
Gynaecological malignancy:				
No	—	—	1.00	1.00
Yes	—	—	4.03 (2.90 to 5.59)	3.71 (2.62 to 5.26)
No of other malignancies:				
0	1.00	1.00	1.00	1.00
1 or 2	9.38 (6.01 to 14.64)	7.79 (4.98 to 12.19)	5.59 (3.82 to 8.19)	5.08 (3.44 to 7.51)

\*Variables entered into both stepwise models were social class at recruitment to oral contraception study, number of cigarettes per day at recruitment, parity, oral contraceptive use, hormone replacement therapy use, history of hypertension, number of cardiovascular morbidities, history of uterine fibroma, gynaecological malignancy, and number of other malignancies. Hazard ratios are presented only for variables identified as independent in each of the final models. Adjustments are made for all variables included in each of the final models.

as the purpose of the oral contraception study is to examine the effects of oral contraception rather than those of hysterectomy. Information about cause of death was mainly based on information from death certificates, often without post mortem. This may have affected cause specific analyses, although many certificates were based on recent illness before death, and any inaccuracies are likely to be non-differential between the groups. The mean length of follow-up was more than 20 years, enabling us to investigate medium to long term mortality risks associated with hysterectomy.

Some women in the original oral contraception study cohort were not flagged, mainly because they left the study before flagging occurred. We have shown that large losses to general practitioner follow-up incurred by the main study have not substantially biased the results for overall mortality.<sup>12</sup> The previous analysis also showed that women in the oral contraception study tend to be healthier than the general population.<sup>12</sup> Thus, although comparisons within the group are valid, caution should be exercised when extrapolating the results to all women after hysterectomy.

Our results may have been affected by residual confounding, partly from the imprecise ascertainment of some factors. Furthermore, some factors were not measured at all, such as use of hormone replacement therapy after hysterectomy, as such information was not available for women who left the oral contraception study after hysterectomy. Current understanding, however, is that hormone replacement therapy may be associated with a balance of higher risk of serious disease (such as breast cancer, stroke, and pulmonary embolism) than benefits (reduced colorectal cancer and fractures of the neck of the femur).<sup>13</sup> More women who have had a hysterectomy use hormone replace-

ment therapy than those who have not.<sup>14</sup> It is unlikely, therefore that the reduced risk of all cause mortality among the hysterectomy group was due to confounding from subsequent use of hormone replacement therapy.

Smoking status was based on information obtained at recruitment to the oral contraception study. The status of many women is likely to have changed. Assuming a pattern similar to national trends,<sup>15</sup> the prevalence of smoking among the cohort will have fallen. The effects of smoking, therefore, are likely to be underestimated.<sup>16</sup> Since we found no significant relation between smoking and hysterectomy, however, our measurement of smoking is unlikely to have affected the risk estimates between hysterectomy and subsequent mortality.

The finding of a lower risk of death among ever users of oral contraceptives in women who were older when they had their hysterectomy (but not younger) was unexpected, and is not readily explained. It may be a chance finding.

We have been able to find only one study that looked at the long term risk of all cause mortality after hysterectomy, and that found no overall effect.<sup>2</sup> In our study, hysterectomy was not associated with a significantly altered risk of death due to cardiovascular disease. Other studies have examined non-fatal cardiovascular outcomes, with conflicting results.<sup>17 18</sup> Some studies have considered the effects of oophorectomy with hysterectomy. We do not know how many of the women in our study had a concurrent unilateral or bilateral oophorectomy. If hysterectomy with oophorectomy has different effects from that without, the effects of different combinations will have been masked. Even if this information was available, it is often difficult to know how many women become

### What is already known on this topic

Hysterectomy is a common operation

Little is known about the long term effects of hysterectomy

### What this study adds

Hysterectomy did not significantly increase a woman's risk of mortality from all causes, cardiovascular disease, and cancer

menopausal soon after hysterectomy. We were therefore unable to carry out separate analyses using menopausal status.

Previous studies have looked at risk of specific cancers after hysterectomy, rather than all cancer mortality. The reduced risk of ovarian cancer after hysterectomy found in one study<sup>19</sup> may have been due to a screening effect, as surgery provides an opportunity to detect abnormal ovaries. Such effects would persist for as long as it takes visible premalignant abnormalities to produce symptoms of cancer.<sup>19</sup> This bias could have occurred in our study, although it is not clear how long such a protective effect might have influenced our risk estimates of all cancer mortality.

Most women in our study had a hysterectomy for non-malignant reasons. They would no longer be at risk of endometrial, cervical, or ovarian cancer if they also had bilateral oophorectomy. Cancers comprise more than a third of deaths in middle aged women, with many at gynaecological sites. The observed lower risk of death (although not statistically significant) from all causes and from cancer among young women who had a hysterectomy was therefore unsurprising. Our results ignore any non-fatal, physical, psychological, and social costs to the individual after hysterectomy. The results should therefore not be used to argue that hysterectomy be used as a public health measure to reduce women's risk of death later in life. Instead, patients should be reassured that hysterectomy will not put their lives at risk later on.

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Competing interests: None declared.

Ethical approval: The study was part of a masters degree submission and received approval from the ethics committee of the London School of Hygiene and Tropical Medicine.

- 1 Vessey MP, Villard-Mackintosh L, McPherson K, Coulter A, Yeates D. The epidemiology of hysterectomy: findings in a large cohort study. *Br J Obstet Gynaecol* 1992;99:402-7.
- 2 Bush TL, Cowan LD, Barrett-Connor E, Criqui MH, Karon JM, Wallace RB, et al. Estrogen use and all-cause mortality. Preliminary results from the lipid research clinics program follow-up study. *JAMA* 1983;249:903-6.
- 3 Luoto R, Auvinen A, Pukkala E, Hakama M. Hysterectomy and subsequent risk of cancer. *Int J Epidemiol* 1997;26:476-83.
- 4 Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *Int J Cancer* 1997;7:948-51.

- 5 Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. *Clin Endocrinol* 1998;49:695-707.
- 6 Kreiger N, Sloan M, Cotterchio M, Kirsh V. The risk of breast cancer following reproductive surgery. *Eur J Cancer* 1999;35:97-101.
- 7 Parazzini F, Braga C, La Vecchia C, Negri E, Acerboni S, Franceschi S. Hysterectomy, oophorectomy in premenopause and risk of breast cancer. *Obstet Gynecol* 1997;90:453-6.
- 8 Gago-Dominguez M, Castelao JE, Yuan J-M, Ross RK, Yu MC. Increased risk of renal cell carcinoma subsequent to hysterectomy. *Cancer Epidemiol Biomark Prevent* 1999;8:999-1003.
- 9 Royal College of General Practitioners. *Oral contraceptives and health*. Tunbridge Wells: Pitman Medical, 1974.
- 10 General Registrar Office. *Classification of occupations*. London: HMSO, 1966.
- 11 World Health Organisation. *International classification of diseases, injuries and causes of death, 8<sup>th</sup> revision*. Geneva: WHO, 1967.
- 12 Beral V, Hermon C, Kay C, Hannaford PC, Darby S, Reeves G. Mortality in relation to method of follow-up in the Royal College of General Practitioners' oral contraception study. In: Hannaford PC, Webb AMC, eds. *Evidence-guided prescribing of the pill*. Lancashire: Parthenon; 1996:327-39.
- 13 Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 2002;360:942-4.
- 14 Moorhead T, Hannaford P, Warskyj M. Prevalence and characteristics associated with use of hormone replacement therapy in Britain. *Br J Obstet Gynaecol* 1997;104:290-7.
- 15 Office for National Statistics. Smoking. In: *Living in Britain. The 2002 general household survey*. www.statistics.gov.uk/lib2002/downloads/smoking.pdf (accessed 25 Aug 2004).
- 16 Owen-Smith V, Hannaford PC, Warskyj M, Ferry S, Kay CR. Effects of changes in smoking status on risk estimates for myocardial infarction among women recruited for the Royal College of General Practitioners' oral contraception study in the UK. *J Epidemiol Community Health* 1998;52:420-4.
- 17 Rosenberg L, Hennekens CH, Rosner B, Belanger C, Rothman KJ, Speizer FE. Early menopause and the risk of myocardial infarction. *Am J Obstet Gynecol* 1981;139:47-51.
- 18 Falkeborn M, Schairer C, Naessén T, Persson I. Risk of myocardial infarction after oophorectomy and hysterectomy. *J Clin Epidemiol* 2000;53:832-7.
- 19 Irwin KL, Weiss NS, Lee NC, Peterson HB. Tubal sterilisation, hysterectomy, and the subsequent occurrence of epithelial ovarian cancer. *Am J Epidemiol* 1991;134:362-9.

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### Corrections and clarifications

#### *Recent developments in inhaled therapy in stable chronic obstructive pulmonary disease*

In the second paragraph of the section "Long acting inhaled bronchodilators" in this Clinical Review by C B Cooper and D P Tashkin (*BMJ* 2005;330:640, 19 Mar), the final sentence should have said that tiotropium increases (not reduces) the time to first exacerbation compared with placebo. (Figure 2 in the article confirms this statement.)

#### *Management of pregnancies with RhD alloimmunisation*

We mixed up images and captions in this Clinical Review by Sailesh Kumar and Fiona Regan (*BMJ* 2005;330:1255-8, 28 May). The caption published with figure 1 should have appeared with figure 2, and the caption for figure 1 should have read: "Ultrasound image showing features of hydrops (skin oedema, hepatomegaly, and ascites)." In the text, these two figures should have been referenced in the Pathophysiology section (the third sentence from the end (fig 1)) and in the seventh sentence of the second paragraph of the Monitoring section (fig 2).

#### *Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial*

An oversight in the editorial process of this paper by J Fairbank and colleagues led to the omission of the international trial number (*BMJ* 2005;330:1233-9, 28 May). The number is ISRCTN88854663.