Cite this article as: BMJ, doi:10.1136/bmj.38483.669178.8F (published 1 June 2005)

Primary care

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 (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

Several new technologies may reduce the need for hysterectomy,[1] yet the procedure remains common in many countries. For example, about 600 000 hysterectomies are carried out in the United States annually,[2] with more than 25% of women having the operation by age 60.[3] Although the number of hysterectomies carried out by the NHS in England and Scotland has fallen by 25% since 1998,[4 5] around 47 500 women still had the procedure in 2002. Around 20% of women in the United Kingdom have a hysterectomy by age 55.[6] 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).[7]

Studies of cardiovascular sequelae have produced conflicting evidence. One study found that hysterectomy with preservation of both ovaries was weakly associated with an increased risk of non-fatal myocardial infarction.[8] Another study found that after hysterectomy with or without preservation of the ovaries, women had an increased 10 year risk of myocardial infarction or coronary death (according to the Framingham score) than women with an intact uterus and ovaries.[9] Conversely, another study found no excess risk of myocardial infarction in premenopausal women after hysterectomy or after unilateral oophorectomy, although it did find an increased risk in post-menopausal women after hysterectomy with or without unilateral oophorectomy.[10]

Another 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 that hysterectomy was not associated with a substantial effect on cancers in general.[11] Several studies have found a reduced risk of ovarian cancer after hysterectomy without bilateral oophorectomy[12 13] and a decreased risk of breast cancer after hysterectomy (with or without oophorectomy).[14 15] Conversely, a study found that renal cell carcinoma was significantly more common among women who had had a hysterectomy compared with those who did not have the operation.[16]

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.[17] The participants' average age at recruitment was 29 years, all were married or living as married, and most (98%) were white. Baseline information collected included details of any previous use of oral contraceptives, social class (as determined by husband's occupation),[18] smoking, parity, and important medical history. Every six months the doctors provided details of any hormonal preparations prescribed, pregnancies and their outcome, surgery, new episodes of illness, and deaths.

During the mid-1970s, 75% of the cohort was flagged at the NHS central registries for future deaths or cancer registrations. The other women could not be flagged because they or their doctor had left the study. 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 (surgical operations and procedures[19] code R690-6, excluding R695)

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 (pseudo-operation) of the same month and year as the hysterectomy carried out on her matched exposed 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; code 2180),[20] gynaecological malignancy (1800, 1820, 1829-31, 1839, 2340, 2341, 2349), other malignancy (1400-1991, 2000-90, excluding 1800, 1820, 1829-31, and 1839), cardiovascular disease (3900-80, 4100-39, 4200-69, 4300-89, 4400-29, 4439-49, 4500, 4511, 4520, 4531, 4539, 4270-99), and hypertension (4000-40). 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 (I-IIIa), manual (IIIb-V), or other (husbands recorded as students or in the armed forces). We compared differences in characteristics between the groups using the χ^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. This was done because age at operation may alter the effect of hysterectomy on outcome, as young women often have hysterectomy for menstrual problems, whereas older women are more likely to have the operation for precancerous or cancerous conditions.

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 ≤ 0.05 (and removed them if they had a P value of ≥ 0.10).

Results

One woman died from a Mullerian tumour more than 26 years after hysterectomy. We found no further information on the death certificate or in the oral contraception study's database to explain the anomaly. We excluded this woman and her matched non-exposed comparator from the cohort, leaving 7410 women for analysis.

Hysterectomy not elsewhere classified (code R696) was the most common type of hysterectomy recorded (2526 women, 68.2%). Both groups had similar characteristics at baseline (table 1). The median age of the cohort 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.

None of the Kaplan-Meier plots for survival from all cause mortality and mortality due to cardiovascular disease or cancer showed significant differences between groups (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 risk of all cause mortality, compared with young women who did not have a hysterectomy (table 2). 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 (table 3). 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, 0.55 to 1.19; table 4). 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, 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.

Table 1 Characteristics of hysterectomy and non-hysterectomy groups.* Values are numbers (percentages) unless stated otherwise

Characteristics	All women (n=7410)	Hysterectomy group (n=3705)	Non-hysterectomy group (n=3705)	P value
Age (years) in relation to median age†:				
≤43.7	3743	1858 (50.1)	1885 (50.9)	0.5
>43.7	3667	1847 (49.9)	1820 (49.1)	
Social class‡:				
Non-manual	2331	1137 (30.7)	1194 (32.2)	0.1
Manual	5013	2529 (68.3)	2484 (67.0)	
Other	66	39 (1.1)	27 (0.7)	
No of cigarettes per day at recruitment:				
0	4205	2134 (57.8)	2071 (56.1)	0.4
1-14	1910	937 (25.4)	973 (26.4)	
≥15	1271	624 (16.9)	647 (17.5)	
Parity†:				
0	335	145 (3.9)	190 (5.1)	0.006
1	881	416 (11.2)	465 (12.6)	
2	2954	1470 (39.7)	1484 (40.1)	
≥3	3238	1673 (45.2)	1565 (42.3)	
Oral contraceptive use†:				
Never	2666	1296 (35)	1370 (37)	0.08
Ever	4744	2409 (65)	2335 (63)	
Hormone replacement therapy use§:				
Never	6990	3489 (94.2)	3501 (94.5)	0.6
Ever	420	216 (5.8)	204 (5.5)	
History of hypertension†:				
No	6593	3281 (88.6)	3312 (89.4)	0.3
Yes	817	424 (11.4)	393 (10.6)	
No of cardiovascular morbidities†:				
0	7005	3477 (93.8)	3528 (95.2)	0.007
1	336	196 (5.3)	140 (3.8)	
≥2	69	32 (0.9)	37 (1.0)	
Uterine fibroma†:				
No	6105	2452 (66.2)	3653 (98.6)	<0.001
Yes	1305	1253 (33.8)	52 (1.4)	
Gynaecological malignancy†:				
No	7102	3418 (92.3)	3684 (99.4)	<0.001
Yes	308	287 (7.7)	21 (0.6)	
No of other malignancies†:				
0	7275	3627 (97.9)	3648 (98.5)	0.08
1 or 2	135	78 (2.1)	57 (1.5)	
Vital status at end of follow-up:				
Alive	6787	3397 (91.7)	3390 (91.5)	0.8
Dead	623	308 (8.3)	315 (8.5)	

*No information at recruitment on smoking for 10 women who had hysterectomy and 14 women who did not. Information on parity missing for one woman in each group.
†All recorded up to and including month of operation or pseudo-operation.
‡At recruitment to oral contraception study.
§Recorded up to and including month before operation or pseudo-operation.

Discussion

In this study, hysterectomy was 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 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 risks of mortality associated with hysterectomy, based on a substantial number of deaths.

Some women in the original oral contraception study cohort were not flagged, mainly because they left the study before flagging occurred. We have shown previously that the large losses to general practitioner follow-up incurred by the main study have not substantially biased the results for overall mortality.[21] The previous analysis also showed that women in the oral contraception study tend to be healthier than the general population.[21] Thus, although comparisons within the group are valid, caution should be exercised when extrapolating the results to all women who have had a hysterectomy. Other studies are needed to confirm or refute our findings.

Our results may have been affected by residual confounding, partly from the imprecise ascertainment of some factors. For example, social class was evaluated in three broad categories, and

Table 2 Factors associated with all cause mortality in women who had or had not had hysterectomy in relation to median age*

	Women aged ≤43.7 years		Women aged >43.7 years	
Characteristic	**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	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 final models. Adjustments are made for all variables included in each of final models.

at one point in time—possibly when effects were not most influential. Furthermore, some factors were not measured at all—for example, use of hormone replacement therapy after hysterectomy, which may affect the risk of subsequent mortality. Information about use of hormone replacement therapy after hysterectomy was not available for women who left the main oral contraception study after the operation. 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 (such as reduced risk of colorectal cancer and fractures of the neck of the femur).[22] More women who have had a hysterectomy than those who have not use hormone replacement therapy.[23] 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.

Table 3 Factors associated with death from cardiovascular disease in women who had or had not had hysterectomy in relation to median age*

	Women aged ≤43.7 years		Women older than median age	
Characteristic	**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	0.93 (0.59 to 1.46)	0.85 (0.54 to 1.33)	0.80 (0.52 to 1.22)	0.80 (0.52 to 1.23)
No of cigarettes per day at recruitment:				
0	1.00	1.00	1.00	1.00
1-14	5.33 (2.55 to 11.15)	5.18 (2.47 to 10.83)	1.54 (0.93 to 2.52)	1.57 (0.95 to 2.59)
≥15	11.95 (5.98 to 23.87)	11.89 (5.95 to 23.78)	1.95 (1.14 to 3.35)	1.95 (1.13 to 3.36)
Oral contraceptive use:				
Never	—	—	1.00	1.00
Ever	—	—	0.67 (0.44 to 1.03)	0.60 (0.39 to 0.92)
History of hypertension:				
No	—	—	1.00	1.00
Yes	—	—	3.46 (2.21 to 5.41)	3.34 (2.11 to 5.29)
No of cardiovascular morbidities:				
0	1.00	1.00	1.00	1.00
1	1.10 (0.27 to 4.48)	1.20 (0.29 to 4.90)	3.01 (1.63 to 5.57)	2.27 (1.21 to 4.26)
≥2	9.50 (2.31 to 38.85)	10.99 (2.66 to 45.43)	5.11 (1.86 to 14.03)	4.00 (1.45 to 11.08)
No of other malignancies:				
0	1.00	1.00	—	—
1 or 2	5.16 (1.62 to 16.41)	3.55 (1.11 to 11.32)	—	—

*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 final models. Adjustments are made for all variables included in each of final models.

Table 4 Factors associated with death from cancer in women who had or 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	0.83 (0.57 to 1.22)	0.81 (0.55 to 1.19)	1.33 (0.94 to 1.80)	1.02 (0.69 to 1.49)
No of cigarettes per day at recruitment:				
0	—	—	1.00	1.00
1-14	—	—	1.55 (1.04 to 2.33)	1.45 (0.96 to 2.19)
≥15	—	—	1.97 (1.27 to 3.06)	1.89 (1.21 to 2.95)
Oral contraceptive use:				
Never	—	—	1.00	1.00
Ever	—	—	0.72 (0.51 to 1.02)	0.67 (0.41 to 0.95)
Gynaecological malignancy:				
No	—	—	1.00	1.00
Yes	—	—	7.71 (5.03 to 11.80)	6.83 (4.29 to 10.87)
No of other malignancies:				
0	1.00	1.00	1.00	1.00
1 or 2	6.96 (3.05 to 15.87)	7.17 (3.14 to 16.39)	7.13 (4.08 to 12.45)	6.02 (3.42 to 10.60)

*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 final models. Adjustments are made for all variables included in each of final models.

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[24] (that is, substantially more middle aged women stopping smoking than starting), the prevalence of smoking among the cohort will have fallen. This was the case in a subset of women in the oral contraception study who participated in a health survey in the mid-1990s.[25] The effects of smoking, therefore, are likely to be underestimated. 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.[7] 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.[8 10] Some studies have considered the effects of oophorectomy with hysterectomy. We do not know how many of the women in our study with hysterectomy had a concurrent unilateral or bilateral oophorectomy. If hysterectomy with oophorectomy has different effects from hysterectomy without oophorectomy, 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 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 such as ovarian and breast cancer after hysterectomy, rather than all cancer mortality. The reduced risk of ovarian cancer after hysterectomy found in one study[26] 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.[26] 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 in life.

We thank Val Angus for extracting the data, the doctors who have contributed to the oral contraception study, and the Chief Scientist Office, Scottish Executive who funded LI as part of a research training fellowship to complete the masters degree of which this study was a component.

Contributors: PCH had the original concept for the study and is also the guarantor. All authors designed the study and devised the data analysis plan. LI analysed the data and drafted the paper. AJL provided statistical advice. All authors commented on drafts and approved the final version of the paper. VA extracted the data from the oral contraception study's database.

Funding: The oral contraception study has received support from the British Heart Foundation, Cancer Research UK, Medical Research Council, Royal College of General Practitioners, Organon Laboratories, Ortho Pharmaceutical, Schering AG, Schering Health Care, Syntex Pharmaceuticals, GD Searle, Syntex Pharmaceuticals, John Wyeth, and Brother.

Competing interests: None declared.

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

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.

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(Accepted 9 May 2005)

doi 10.1136/bmj.38483.669178.8F

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