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ORIGINAL ARTICLE

Risk assessment of dementia after hysterectomy: Analysis of 14-year data from the National Health Insurance Research Database in Taiwan

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Abstract

Background: Anesthesia and surgery may increase the risk of dementia in the elderly, but the higher prevalence of dementia in women and other evidence suggest that dementia risk increases in younger women undergoing hysterectomy. In this study, we assessed the risk of dementia after hysterectomy.

Methods: Hysterectomies registered in the National Health Insurance Research Database from 2000 to 2013 were evaluated using a retrospective generational research method. Multivariate Cox regression analysis was used to assess the effect of age at surgery, anesthesia method, and surgery type on the hazard ratio (HR) for the development of dementia.

Results: Among 280 308 patients who underwent hysterectomy, 4753 (1.7%) developed dementia. Age at surgery and anesthesia method were associated with the occurrence of dementia, independent of surgery type. Among patients 30–49 years of age, general anesthesia (GA) was associated with a higher risk of dementia than spinal anesthesia (SA). The HR for GA was 2.678 (95% confidence interval [CI] = 1.269–5.650) and the risk of dementia increased by 7.4% for every 1-year increase in age (HR = 1.074; 95% CI = 1.048–1.101). In patients >50 years of age, the HR for GA was 1.206 (95% CI = 1.057–1.376), and the risk of dementia increased by 13.0% for every 1-year increase in age (HR = 1.130; 95% CI = 1.126–1.134).

Conclusion: The risk of dementia in women who underwent hysterectomy was significantly affected by older age at surgery, and the risk might not increase linearly with age, but show instead an S-curve with exponential increase at about 50 years of age. Although less significant, GA was associated with higher risk than SA, and the effect of the anesthesia method was greater in patients <50 years of age. In contrast, the surgical procedure used was not associated to the risk of dementia.

Keywords: Anesthesia; Dementia; Hysterectomy

1. INTRODUCTION

Dementia has become a serious global issue in our aging society, and affects almost one-fourth to one-third of people 90 years of age and older.[1] Data from both China and the United Kingdom revealed significant sex differences, with higher incidence of dementia in women vs men.[2,3] Both sex and gender differences may play an important role in the development of dementia through genetics, hormones, social functions, etc.[4–7] Phung et al[8] tried to determine whether dementia is associated with hysterectomy, which is a very common procedure, with a stable rate of 5.1 to 5.8 hysterectomies per 1000 civilian women residing in the United States.[9]

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Previous studies of oophorectomy showed increased risk of Alzheimer's disease (AD)[10–12] and decline in overall cognitive function[13,14] associated to surgical menopause at an earlier age. On the other hand, Geerlings et al reported that a long reproductive period was associated with dementia.[15] There is insufficient evidence to support a correlation between long-term exposure to female hormones and reduced risk of dementia in clinical trials[16] due to small sample sizes and high heterogeneity, although some studies supported a correlation between deficiency in female hormones and cognitive aging.[17,18] Further studies to delineate the differences in the effects of endogenous and exogenous estrogen on the brain are needed, even though empirical results have demonstrated the neuroprotective effect of estrogen.[19,20]

Many previous studies have shown that anesthesia and surgery can increase the risk of developing dementia.[21] Using the longitudinal National Health Insurance Database of Taiwan, a case-control study[22] indicated a dose-dependent relationship of general anesthesia (GA) with dementia, especially with comorbid diabetes mellitus, hypertension, and stroke. Another cohort study[23] also concluded that the risk of dementia increased in patients who received anesthesia and surgery, but had limited ability to confirm the causality relationship between anesthesia or surgery and dementia. A stationary hysterectomy rate (~268–303 per 100 000 women) was reported in Taiwan from 1996 to 2001, although surgical procedures changed.[24] Therefore, we hypothesized that hysterectomy would be suitable to analyze the effects of different factors on dementia.

In this study, we aimed to use databases collected in Taiwan to evaluate the risk of dementia in patients who underwent hysterectomy and assess the effects of age at surgery; anesthesia method, including GA or regional anesthesia such as spinal anesthesia (SA) or epidural anesthesia (EA); and different surgery types, such as conventional or minimally invasive surgery.

2. METHODS

2.1. Study subjects

In this study, we considered patients >30 years of age who underwent hysterectomy for benign causes with anesthesia records, included in the retrospective cohort study of the National Health Insurance Database from 2000 to 2013, and we excluded the cases with missing data and double operation records. We conducted a longitudinal observation study to evaluate the effects on dementia of anesthesia methods (GA, SA, or EA), surgical method (conventional abdominal total hysterectomy (ATH), vaginal total hysterectomy (VTH), or laparoscopic-assisted vaginal hysterectomy (LAVH)), and age at surgery (<50 or >50 years). The data were obtained from the health and welfare database of the Ministry of Health and Welfare Collaboration Center of Health Information Application. This study was approved by the Research Ethics Review Committee of the Far Eastern Hospital. The requirement for informed consent was waived due to the retrospective nature of the study. All data including secondary data, personal basic information, and basic information on the medical institution (medical institution code) were encrypted. The data files used were as follows:

(1) National Health Insurance Prescription and Treatment Detail Files-Emergency outpatient (used for dementia data)
(2) National Health Insurance Prescription and Treatment Detail Files-Western medicine inpatient (used for dementia, hysterectomy, or oophorectomy data)
(3) National Health Insurance Prescription and Treatment Order File-Inpatient (for GA, SA, or EA data)
(4) Cause of death statistics files

Survival analysis was used to assess the correlation between anesthesia method and dementia. In case of mortality during the observation period, the patient was observed until death.

The variables used from the cause of death statistics file were as follows:

1. ID: Identification card number
2. D_DATE: Date of death

2.2. Study definitions

(1) Total hysterectomy: defined by the following inpatient surgery codes
- 68.4 ATH
- 68.5 VTH
- 68.51 LAVH

(2) Anesthesia method: defined by the following inpatient medical order codes

- SA: 96007C or 96008C
- Semi-opened or semi-closed mask inhalation GA: 96004C, 96017C, 96018C, or 96019C
- Semi-closed or closed-circulative intratracheal intubation GA: 96020C, 96021C, or 96022C
- EA: 96005C or 96006C

(3) Oophorectomy: defined by the following inpatient surgery code

- 65.51 Bilateral salpingo-oophorectomy (BSO)
- 65.53 Laparoscopic Bilateral salpingo-oophorectomy (laparoscopic BSO)

(4) Dementia: defined according to the ninth edition of the International Classification of Diseases (ICD-9-CM) in the outpatient list file and inpatient list file and including the following ICD-9-CM codes:

- 331 other cerebral degenerations
- 290 senile and presenile organic psychotic conditions
- 294.1 dementia in conditions classified elsewhere

Postoperative dementia was diagnosed for cases with two or more outpatient visits with the ICD-9-CM codes 331, 290, or 294.1, and time elapsed from hysterectomy to the onset of dementia of at least 3 months.

2.3. Statistical methods

2.3.1. Descriptive statistics

The number of patients, percentage, mean, SD, maximum value, and minimum value were used in descriptive statistics. Chi squared test, independent *t*-test, and 1-way ANOVA were used to assess intergroup differences in categorical variables or continuous variables with statistical significance defined as *p*-value < 0.05.

2.3.2. Survival analysis

Kaplan-Meier and Cox regression were used to analyze the risk of dementia after hysterectomy. We estimated the mean time elapsed from surgery to dementia onset and used multivariate Cox regression analysis with hazard ratio (HR) as the evaluation marker to assess the effects of anesthesia method, age at surgery (30–49 years vs ≥50 years), and surgery type on dementia.

2.3.3. Epidemiological markers

Incidence density (ID) was defined as the number of dementia patients divided by the total observation period (in person years). If the patient developed dementia or died before the study ended, the observation end date was the date of dementia onset or death. Thus, the risk of developing dementia can be calculated for every year. The incidence density is calculated as follows:

$$\frac{\text{Incident cases}}{\text{Person years}} \times 1000$$

and represents the number of people per 1000 who developed dementia every year. The incidence ratio (IDR) is defined as the ratio of the incidence densities between two populations. The formula for calculating its 95% confidence interval (CI) is as follows:

$$\text{IDR} \times e^{\pm 1.96\sqrt{\frac{1}{I_0}+\frac{1}{I_1}}}$$

where I_0 and I_1 represent the number of people who developed the disease in the two populations.

2.3.4. Preprocessing data

For the definition of dementia, we have referenced the 2011 Ministry of Health and Welfare dementia prevalence survey. We first ran the prevalence results in the database and found that this is compatible with the prevalence obtained from our defined diagnosis codes. Dementia prevalence only starts to increase at 65 years of age (Supplementary Figure 1 http://links.lww.com/JCMA/A49). The cumulative incidence for post-hysterectomy dementia increases to 95% of the maximum value at 8.6 years after surgery (Supplementary Figure 2 http://links.lww.com/JCMA/A49).

3. RESULTS

3.1. Distribution of dementia in different age-groups at surgery

Among the patients who underwent total hysterectomy from 2000 to 2013, the proportion of patients who developed dementia increased with age at surgery: This proportion among those who underwent total hysterectomy at 30–40 years was 0.17%, while for age at surgery 65–69, 70–74, 75–79, 80–84, and 85 and above the proportion was 8.9%, 12.8%, 16.0%, 15.1%, and 16.2%, respectively. The proportion of patients who developed dementia showed large differences between the age-groups at surgery, with statistical significance (Table 1).

A graphical representation of the incidence of dementia as a function of age at surgery showed an S-shaped increase. We calculated the second derivative of the model function to obtain the inflection point. As a result, the threshold age of the effect of surgery was 57.6 years and the inflection point of the curve was 66 years, indicating that 57.6–66 years is a critical developmental period for dementia (Fig. 1).

3.2. Dementia incidence in patients with different characteristics

Table 2 shows the dementia ID and IDR in patients 30 years of age and older who underwent total hysterectomy. Based on the lowest age group (30–34 years) of patients who underwent total hysterectomy as the reference group, the risk of developing dementia was significantly higher in patients 45 years of age and above compared with the reference group. The IDR for patients 45–49 years of age and above 85 years was 2.65 (95% CI = 1.36–5.16) and 264.31 (95% CI = 131.64–530.72), respectively. The result indicated that the risk of developing dementia increased with increasing age at surgery, especially >45 years.

Table 1.

Distribution of dementia in different age groups at surgery

		Non-dementia	Dementia	
Age (years)	n	N (%)	N (%)	p
30–34	7056	7047 (99.9)	9 (0.1)	<0.001
35–39	28 874	28 823 (99.8)	51 (0.2)	
40–44	85 273	85 099 (99.8)	174 (0.2)	
45–49	76 935	76 705 (99.7)	230 (0.3)	
50–54	38 144	37 938 (99.5)	206 (0.5)	
55–59	12 981	12 751 (98.2)	230 (1.8)	
60–64	9294	8841 (95.1)	453 (4.9)	
65–69	7843	7147 (91.1)	696 (8.9)	
70–74	5689	4959 (87.2)	730 (12.8)	
75–79	3226	2709 (84)	517 (16.0)	
80–84	1196	1015 (84.9)	181 (15.1)	
85–89	402	337 (83.8)	65 (16.2)	
Total	276 913	273 371 (98.72)	3542 (1.28)	

The chi squared test was used for the analysis. Dementia was defined as new cases 3 months after surgery.

The incidence density of dementia in patients 50 years of age and older shows an almost perfectly linear relationship with age. A predictive model of the incidence density and age was constructed using linear regression, leading to the equation $y = 6.0143x - 8.9018$, where y is the incidence density, x is the age group. The R^2 of the model is 0.9771 (Pearson correlation = 0.98845).

3.3. Multivariate Cox regression analysis of the correlation between patients with different characteristics and dementia

In multivariate Cox regression, shown in Table 3, age at surgery turned out to be much more significant than anesthesia method, while there was no significant difference between the surgical methods. In patients 30–49 years of age, based on SA as the reference group, the risk of developing dementia was higher with GA (HR = 2.678, 95% CI = 1.269–5.650), and with every 1-year increase in age, there was a 7.4% increase in the risk of dementia (HR = 1.074, 95% CI = 1.048–1.101).

In patients >50 years of age, based on SA as the reference group, the risk of developing dementia was higher with GA (HR = 1.206, 95% CI = 1.057–1.376), and with every 1-year increase in age, there was a 13.0% increase in the risk of dementia of (HR = 1.130, 95% CI = 1.126–1.134).

Compared with the significant effects of surgical age on the incidence of dementia after hysterectomy, the effects of anesthesia methods are relatively low. In addition, the effects of GA are greater in patients <50 years and lower in patients >50 years (Supplementary Figure 3 and 4 http://links.lww.com/JCMA/A49).

As the number of patients, 30–49 years of age, who underwent oophorectomy was zero, convergence of the model including this variable was not achieved, and the variable was removed.

4. DISCUSSION

We conducted a cohort-based study of hysterectomy data to evaluate the effects of age at surgery, anesthesia methods, and surgical methods on dementia. We found that the risk of post-hysterectomy dementia was affected significantly by older age at surgery. The data suggest that the risk does not increase linearly with age, but shows instead an S-curve, with an exponential increase around 50 years of age. Although less significant, GA was associated with a higher risk than SA, and the effect of the anesthesia method was greater in patients <50 years of age. In contrast, the surgical procedure used was not associated to the risk of dementia.

Hysterectomy is one of the most commonly performed surgical procedures in women of reproductive age, and has been shown to accelerate menopause by 3–4 years even without oophorectomy, resulting in premature estrogen withdrawal. A Danish study revealed the age-dependent effects of premature estrogen deficiency on dementia and showed a dosage-dependent action of premature estrogen deficiency on the risk of dementia.[8] With the aim of clarifying the effect of age (before or after menopause) and different anesthetic or surgical methods, we chose to study hysterectomy, as in the Danish study. However, our results were different from the ones of the Danish study, which reported higher dementia risk in younger women. Although a direct comparison between Taiwan and Denmark is problematic, we may add a control group, as in the Danish study, in the future.

A previous study[23] used the National Health Insurance database to identify 100 000 patients at 10-year follow-up, and compared patients who underwent anesthesia and surgery with a control group. The study reported that the HR of dementia in patients who underwent anesthesia and surgery was 1.99 and inferred that anesthesia and surgery increased

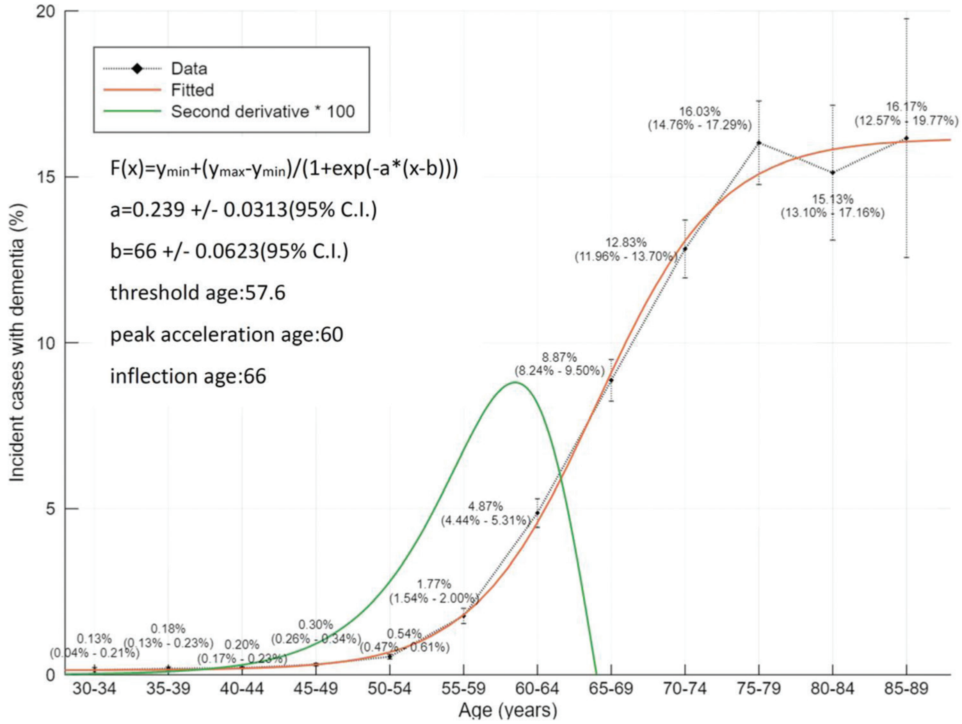

Fig. 1. Relationship between the incidence of dementia and age at total hysterectomy.

Table 2.

Incidence density (ID) of dementia in patients 30 years and older with different characteristics

Variable	N	Mean follow-up duration (person years)	Total follow-up duration (person years)	Number of dementia patients	ID	IDR	95% CI	Significance
Anesthesia method								
SA	10 088	8.35	84 235	266	3.16	1.00	—	
GA	259 270	6.99	1 812 557	3096	1.71	0.53	0.469–0.642	—
EA	7555	8.96	67 720	180	2.66	0.84	0.698–1.019	
Surgical method								
ATH	148 136	7.00	1 036 955	1609	1.55	1.78	1.589–1.989	+
VTH	42 918	11.54	495 295	1555	3.14	3.44	3.078–3.854	+
LAVH	85 859	5.03	432 262	378	0.87	1.00	—	
Age at surgery (years)								
30–34	7056	8.02	56581	9	0.16	1.00	—	
35–39	28 874	7.91	228 378	51	0.22	1.40	0.71–2.85	
40–44	85 273	7.34	626 236	174	0.28	1.75	0.89–3.41	
45–49	76 935	7.08	544 916	230	0.42	2.65	1.36–5.16	+
50–54	38 144	6.55	249 878	206	0.82	5.18	2.66–10.10	+
55–59	12 981	5.98	77 599	230	2.96	18.63	9.57–36.26	+
60–64	9294	6.65	61 780	453	7.33	46.09	23.82–89.15	+
65–69	7843	7.05	55 286	696	12.59	79.13	41.00–152.72	+
70–74	5689	6.68	37 976	730	19.22	120.82	62.61–233.14	+
75–79	3226	5.84	18 831	517	27.45	172.56	89.28–333.54	+
80–84	1196	4.60	5505	181	32.88	206.65	105.81–403.59	+
>85	402	3.85	1546	65	42.05	264.31	131.64–530.72	+

+ = Positive statistical significance; – = Negative statistical significance; ATH = abdominal total hysterectomy; EA = epidural anesthesia; GA = general anesthesia; IDR = incidence ratio; LAVH = laparoscopic assisted vaginal hysterectomy; SA = spinal anesthesia; VTH = vaginal total hysterectomy.

the risk of developing dementia. However, whether the risk was correlational or casual was not determined, nor was it possible to distinguish between the effects of surgery itself and anesthesia on the risk of dementia. In addition, different surgery types showed different levels of risk, with higher risk associated to thoracic surgery, but there was no consistency in the risk of developing dementia compared with the outcome of other surgery types. It is likely that age at surgery, which was in fact the most significant risk factor, was overlooked as a confounding factor.

Table 3.

Multivariate Cox regression analysis of the risk of dementia as a function of patient characteristics, stratified using the age cutoff point of 50 years

	30–49 years				>50 years			
Variable	**HR**	**95% CI (lower limit)**	**95% CI (upper limit)**	***p***	**HR**	**95% CI (lower limit)**	**95% CI (upper limit)**	***p***
Anesthesia method				0.0107				0.0208
SA	1.000	—	—		1.000	—	—	
GA	2.678	1.269	5.650	0.0097	1.206	1.057	1.376	0.0054
EA	1.603	0.610	4.214	0.3385	1.167	0.961	1.416	0.1193
Age	1.074	1.048	1.101	<0.0001	1.130	1.126	1.134	<0.001
Surgical method				0.3393				0.8158
ATH	1.098	0.857	1.406	0.4606	0.966	0.848	1.099	0.5953
VTH	1.230	0.927	1.630	0.1509	0.957	0.837	1.095	0.5235
LAVH	1.000	—	—		1.000	—	—	

ATH = abdominal total hysterectomy; CI = confidence interval; EA = epidural anesthesia; LAVH = laparoscopic assisted vaginal hysterectomy; SA = spinal anesthesia; GA = general anesthesia; HR = hazard ratio; VTH = vaginal total hysterectomy.

In our study, we only considered total hysterectomy cases and compared different surgery types and anesthesia methods. However, in multivariate analysis, age at surgery was by far the most significant risk factor. Therefore, we hypothesize that in women, above the age of 50 years, age at surgery is an important factor influencing postoperative dementia. Although surgery is a trigger to cause dementia, its effect is not strongly related to the surgical or anesthesia methods.

In the field of anesthesiology, some evidence has been shown of postoperative cognitive dysfunction (POCD) and dementia.[25,26] POCD in patients undergoing anesthesia and surgery is a well-known clinical phenomenon.[27] As early as 1955, Bedford[28] described the adverse events of anesthesia in the brain of elderly people and recognized the need to determine the patients' preoperative cognitive status to determine POCD. In addition, factors including older age, preexisting brain, heart, and vascular disease, low educational level, and invasive surgery can increase the risk of POCD,[29] and the same factors are associated to dementia. POCD is characterized by transient confusion after surgery, and is associated with postoperative recovery status. The immune response triggered by surgery is one of the multiple etiologies of POCD, and may also cause postoperative dementia. Meticulous care by anesthetists and surgeons can reduce the occurrence of intraoperative and postoperative complications, thereby decreasing the risk of POCD, which may in turn decrease the risk of developing dementia.[30]

The effects of anesthesia methods on POCD are still controversial.[31,32] Instead, surgery itself could be the primary cause affecting cognition. Therefore, the effects of anesthesia and surgery on POCD should be interpreted separately. A previous study showed that elderly people who underwent extracorporeal shock wave lithotripsy also developed POCD.[33] However, those patients did not receive GA. These results support the hypothesis that POCD may be directly associated with medical care outcomes, and not with GA. Some previous studies on surgical methods[34] reported that minimal invasive abdominal surgery did not affect postoperative cognition, which corroborates the results obtained in the present study.

Besides the absence of a control group, our study has some limitations. Although we anticipate to examine whether concurrent oophorectomy can be used as an index of hormonal change, the number of patients who underwent concurrent oophorectomy was too small and did not include patients <50 years of age. The statement that the risk of dementia was significantly higher in postmenopausal patients who underwent surgery was made based on age. Moreover, we did not have the actual female hormone level data needed to correlate the risk of dementia to estrogen deficiency. A previous study[35] examined the effects of corticosteroid hormones produced by the adrenal glands on POCD. However, there are no studies examining the effects of female hormones on cognitive dysfunction after surgery in postmenopausal women. Although many studies examined cognitive decline in postmenopausal women, clinical trials on the efficacy of female hormone supplementation obtained disappointing results.[36]

The significant effect of age at hysterectomy on the postoperative development of dementia may be attributed to female hormones. We hypothesize that a decrease in the threshold value for developing postoperative dementia occurs in the 10-year period after menopause, which support the healthy cell bias of 17β-estradiol (E2) replacement hypothesis.[37] Therefore, the timing of hormonal therapy is of vital importance to the occurrence of menopause. The use of hormonal therapy before and after menopause can maintain health status, as E2 is a neurological and cardiovascular protective factor. However, delayed E2 treatment after menopause, or lack of long-term E2 supply (such as 10 years) may result in harmful effects to women's health and increase the risk of developing venous thromboembolism, ischemic stroke, and dementia.[38]

In conclusion, this study confirms that dementia has become a serious issue in our aging world. Global epidemiologic data reveal significant sex differences, with higher incidence of dementia in women than men, a trend which is also observed in Taiwan. We could also confirm that the incidence of dementia significantly increases after hysterectomy above a threshold age of about 50 years, with many possible factors, including surgical trigger, anesthetic agents, and female hormones, contributing to the development of dementia. Our study used observational descriptive statistics and risk factor analysis on women who underwent hysterectomy. Therefore, more evidence is required to confirm the effects of surgery and anesthesia on dementia in the general population. Currently, we first proposed that surgical age has significant meaning. However, the available data did not allow us to determine how other factors, such as genetic differences, social factors, or differences in education level or physical exercise, affect the occurrence of dementia after hysterectomy. In the future, we will conduct controlled studies and data mining[39] to clarify whether such causes of dementia are associated with surgery and anesthesia. In addition, we plan to examine whether dementia outcomes are different after surgery, and compare the findings with those of previous studies.[40,41]

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