科技部補助專題研究計畫成果報告
期末報告

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肥胖與年齡對於子宮內膜癌死亡率的影響：台灣與美國的差異分析

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報 告 附 件 ： 出席國際學術會議心得報告

中 華 民 國 107 年 10 月 25 日

中 文 摘 要 ： 過去研究針對子宮內膜癌與肥胖的因果關係已經被廣泛的研究並獲
得證實；但針對台灣婦女罹患子宮內膜癌風險與肥胖對其死亡率和
預期壽命的影響，則尚未得到充分的研究。本研究規劃中台灣三處
醫學中心子宮內膜癌病患資料(中山醫學大學附設醫院、台中榮民總
醫院、中國醫藥大學附設醫院)（資料期間：1995-2016年）。根據樣
本不同身體質量指數(BMI)狀態，分別使用Gamma Frailty Model 與
Gompertz Baseline兩種存活模式，分析台灣婦女罹患子宮內膜癌的
年齡估計死亡率及其壽命年損失的預測。關於計算生命年限的設計
，本研究採用三處醫學中心樣本資料的生命規劃範圍與死亡率估計
數為基礎，這種方法不受到後續追蹤個案生命年不同的長度限制
，有別於生命表統計推論群體的存活經驗，可以反應本研究問題更
客觀的事實。規劃在美國Missouri Baptist Medical Center同步進
行資料分析，加以比較兩國的差異。研究結果顯示，子宮內膜癌根
據肥胖程度增加死亡的風險，根據年齡和肥胖狀況將壽命縮短1至
16歲。死亡的相對危險度隨著肥胖程度的增加而增加。兩個國家的
55歲以下肥胖婦女被預測損失最多生命年；美國組（15.1歲）比台
灣組（11.6歲）損失最多生命年。與子宮內膜癌相關的生命年數減
少對於肥胖多於肥胖少的婦女以及55歲以下婦女和76歲或76歲以上
婦女比56歲至75歲婦女更加明顯。公共衛生促進活動應該更加重視
對這些目標人群的肥胖預防和控制。

中文關鍵詞 ： 子宮內膜癌，肥胖，死亡率，身體質量指數

英 文 摘 要 ： The relationship between obesity and endometrial cancer has
been extensively investigated, yet its impact on mortality
and life expectancy of a general Taiwanese female
population has not been well studied. The purpose of this
proposal is to investigate the mortality risks associated
with endometrial cancer according to body mass index (BMI)
and age level to predict life years lost in a general
female population in Taiwan. Data (electronic medical
record) from four medical centers: Chung-Shan Medical
University Hospital (CSMUH), Taichung Veterans General
Hospital (TVGH), China Medical University Hospital (CMUH)
and Washington Univ. in St. Louis (Missouri Baptist Medical
Center, MBMC) will be used in this project. Surveillance
Survey in Taiwan and United States were conducted from 1995
to 2016. A survival model with gamma frailty and gompertz
baseline will be use to estimate relative risks of total
mortality and project life years lost associated with
endometrial cancer by obesity status and age.

Endometrial cancer increased risk of mortality depending on
degree of obesity and decreased life years by 1 to 16 years
depending on age, and obesity status. Relative risks for
death increased with degree of obesity. Obese women under
age 55 across both national groups were predicted to lose
the most life years; USA group (15.1 y) more than Taiwan

group (11.6 y) lost the most life years. The number of life years lost associated with endometrial cancer was more marked for more obese than for less obese women and for women under age 55 and women aged 76 or older than for women aged 56 through 75. Public health promotion should put more emphasis on the prevention and control of obesity for these target populations.

科技部補助專題研究計畫成果報告

（□期中進度報告/■期末報告）

肥胖與年齡對於子宮內膜癌死亡率的影響：台灣與美國的差異分析

計畫類別：■個別型計畫　　□整合型計畫
計畫編號：MOST　106-2221-E-040-010-
執行期間： 106 年 8 月 1 日至 107 年 7 月 31 日

執行機構及系所：中山醫學大學醫學資訊學系

計畫主持人：張啟昌

本計畫除繳交成果報告外，另含下列出國報告，共 _1_ 份：
□執行國際合作與移地研究心得報告
■出席國際學術會議心得報告

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中　華　民　國　107　年　11　月　25　日

1. BACKGROUND AND RATIONALE

Endometrial cancer is one of the most common gynecological malignancies in the developed world. The International Agency for Research on Cancer (IARC), reported in 2016 an estimated 199,000 women living with endometrial cancer worldwide, and 50,000 women died of this cancer. Endometrial cancer is the fourth most common cancer among women in the United States and Europe (Ferlaya et al., 2013).

In Taiwan, endometrial cancer is the second most common neoplasm, following cervical cancer, in the female genital tract (Ministry of Health and Welfare (MOHW), 2016). According to the data of Taiwan Cancer Registry, the annual incidence rate of endometrial cancer was 11.25 cases per 100,000 women in 2010, as compared to 1.69 cases per 100,000 women in 1980 (Figure 1 and Table 1). It is estimated that there will be more than 2,400 new cases in 2014

Figure 1 Incidence Rates of Cervical Cancer, Endometrial Cancer, Ovarian Cancer in Taiwan, 1979-2013

① Endometrial Cancer   ② Cervical Cancer   ③ Ovarian Cancer
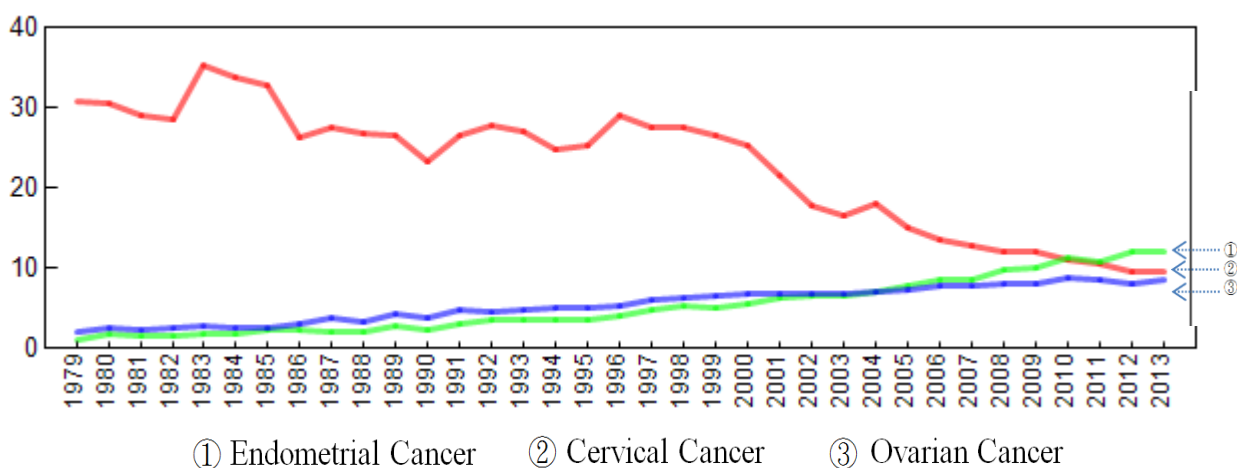
Source: The Bureau of Health Promotion (BHP), Taiwan, 2016

Endometrial cancer is the most common invasive gynecologic cancer in U.S. (PDQ Cancer Information Summaries, 2015) an estimated 54,870 cases of cancer of the uterine corpus (body of the uterus) are expected to be diagnosed in 2015. Cancer of the uterine corpus is often referred to as endometrial cancer because most cases (92%) occur in the endometrium (lining of the uterus). Incidence rate have increased by 2.4% per year from 2007 to 2013 (Figure 2 and Table 2). An estimated 10,170 deaths are expected in 2015. From 2007 to 2013, death rates for cancer of the uterine corpus increased by 1.9% per year. There is no standard or routine screening test for women at average risk. Most cases (68%) are diagnosed at an early stage because of postmenopausal bleeding. Women are encouraged to report any unexpected bleeding or spotting to their physicians. The American Cancer Society recommends that women with known or suspected Lynch syndrome be offered annual screening with endometrial biopsy and/or transvaginal ultrasound beginning at age 35. Higher body weight adversely affects survival, whereas physical activity is associated with improved survival.

The 5-year survival for endometrial cancer depends on cancer stage at diagnosis. In general, it is 81.5% (SEER, 2007-2011). However, the recurrence rate for International Federation of Gynecology and Obstetrics (FIGO) stage II to stage IV disease with modern multimodality treatment is approximately 25% (American Cancer Society, 2015). For early-stage disease, surgery alone or in combination with local therapy is generally curative. Once the primary treatment has failed, the opportunity of secondary cure is slim.

The natural history of endometrial cancer has developed through evaluation of the patterns of spread (American Cancer Society, 2016). Stage I endometrial cancer is cancer confined to the corpus uteri; Stage II endometrial cancer involves the corpus and the cervix, but has not extended outside the uterus; Stage III endometrial cancer extends outside of the uterus but is confined to the true pelvis; Stage IV endometrial cancer involves the bladder or bowel mucosa or has metastasized to distant sites. All patients are usually classified further according to the extent or stage of disease so that therapies may be tailored to the particular disease stage. The treatment of endometrial cancer requires a complex therapeutic approach, consisting of surgery, radiotherapy, chemotherapy and/or hormonal therapy. Fortunately, most women are diagnosed at an early stage and are treated by hysterectomy and surgical staging alone. Patients with advanced-stage endometrial cancer represent 10-15% of all newly diagnosed cases but account for over half of all uterine cancer related deaths, with a survival rate as 5-20%. Specifically, for patients with stage III or stage IV and for those with recurrent endometrial cancer, the prognosis remains poor and the optimal adjuvant therapy is yet to be established. A subset of these patients may benefit from hormonal manipulation, systemic chemotherapies, or combination treatment with volume-directed radiotherapy and systemic chemotherapy. The choice of therapy depends on the extent of residual disease after initial surgery, site and nature of the recurrence, prior therapy used, and intent of treatment, be it curative or palliative.

Table 1 Statistical Trend of Cervical Cancer, Endometrial Cancer and Ovarian Cancer in Taiwan from 1979-2013 (Source: The BHP, Taiwan, 2016)

Years	Cervical Cancer					Endometrial Cancer					Ovarian Cancer				
	Cases	Avg. Age	Med. Age	Incidence Rate	Rate of Cancer	Cases	Avg. Age	Med. Age	Incidence Rate	Rate of Cancer	Cases	Avg. Age	Med. Age	Incidence Rate	Rate of Cancer
1979	1,790	50.75	50	30.70	32.20%	58	51.24	54	1.00	1.04%	129	46.73	49	2.08	2.32%
1980	1,827	51.04	51	30.54	28.06%	99	53.65	54	1.69	1.52%	162	46.62	50	2.50	2.49%
1981	1,771	52.37	52	29.09	26.39%	89	55.49	55	1.49	1.33%	156	47.56	50	2.38	2.32%
1982	1,800	52.6	52	28.62	26.98%	94	52.51	54	1.47	1.41%	175	46.73	49	2.56	2.62%
1983	2,279	52.85	53	35.28	28.79%	121	53.37	52	1.87	1.53%	200	44.17	47	2.78	2.53%
1984	2,262	52.51	52	33.74	28.40%	124	52.32	53	1.84	1.56%	179	48.74	51	2.50	2.25%
1985	2,260	53.34	53	32.77	26.79%	161	54.02	54	2.34	1.91%	191	45.24	47	2.51	2.26%
1986	1,892	52.58	53	26.27	23.25%	157	53.27	54	2.19	1.93%	239	47.7	48	3.09	2.94%
1987	2,064	53.27	54	27.66	21.18%	143	51.6	53	1.92	1.47%	309	45.95	48	3.81	3.17%
1988	2,063	53.01	53	26.80	21.52%	162	51.05	53	2.06	1.69%	265	45.84	48	3.19	2.76%
1989	2,119	53.14	54	26.54	18.95%	213	53.23	54	2.68	1.90%	367	47.29	49	4.33	3.28%
1990	1,921	53.82	55	23.33	18.58%	181	52.29	52	2.21	1.75%	334	46.78	49	3.81	3.23%
1991	2,275	53.6	54	26.65	17.55%	262	51.44	52	3.02	2.02%	415	47.72	49	4.67	3.20%
1992	2,480	52.45	52	27.83	17.24%	311	52.38	53	3.58	2.16%	407	47.94	48	4.45	2.83%
1993	2,471	53.59	54	27.05	16.60%	325	52.26	53	3.60	2.18%	462	48	48	4.91	3.10%
1994	2,360	53.56	54	24.93	15.45%	327	52.57	53	3.52	2.14%	480	48.16	48	4.94	3.14%
1995	2,461	53.77	54	25.21	15.30%	343	51.9	53	3.58	2.13%	514	47.26	47	5.15	3.20%
1996	2,942	53.67	54	29.07	15.89%	399	52.17	52	4.04	2.16%	546	48.04	48	5.34	2.95%
1997	2,871	54.26	54	27.52	14.01%	495	52.37	52	4.84	2.42%	633	49.1	48	6.02	3.09%
1998	2,976	54.61	54	27.61	13.38%	549	52.5	52	5.21	2.47%	677	50.3	49	6.22	3.04%
1999	2,965	54.61	53	26.51	12.31%	553	52.6	51	5.07	2.30%	732	48.82	48	6.52	3.04%
2000	2,916	55.22	55	25.42	11.60%	627	52.6	52	5.56	2.50%	790	49.52	49	6.89	3.14%
2001	2,552	55.89	54	21.52	9.96%	714	53.79	53	6.17	2.79%	789	49.21	49	6.69	3.08%
2002	2,193	56.11	54	17.92	8.29%	786	52.65	51	6.50	2.97%	817	51.26	50	6.75	3.09%
2003	2,097	56.03	54	16.66	7.83%	815	52.74	52	6.48	3.04%	862	50.63	50	6.91	3.22%
2004	2,370	56.12	53	18.13	7.87%	921	52.73	51	7.11	3.06%	889	51.68	51	6.98	2.95%
2005	2,025	56.64	54	15.09	6.58%	1,031	52.78	52	7.69	3.35%	940	50.79	50	7.17	3.05%
2006	1,884	56.49	54	13.60	5.81%	1,188	53.65	53	8.65	3.67%	1,037	51.52	51	7.74	3.20%
2007	1,817	56.61	54	12.70	5.33%	1,195	52.93	53	8.47	3.51%	1,083	51.21	51	7.87	3.18%
2008	1,781	56.74	54	12.16	4.99%	1,441	53.43	53	9.88	4.04%	1,130	51.83	51	7.93	3.17%
2009	1,815	57.63	55	12.00	4.63%	1,528	53.82	53	10.14	3.90%	1,155	51.13	51	8.00	2.95%
2010	1,703	57.86	56	10.95	**4.19%**	1,757	54.06	54	11.39	**4.32%**	1,276	51.84	52	8.68	**3.14%**
2011	1,688	57.53	56	10.61	↓ 4.09%	1,729	54.15	54	10.91	↑ 4.18%	1,260	51.06	51	8.42	↓ 3.05%
2012	1,567	57.57	56	9.60	↓ 3.63%	1,936	54.56	55	11.96	↑ 4.49%	1,236	52.53	52	8.04	↓ 2.87%
2013	1,579	57.87	56	9.46	↓ 3.54%	2,011	54.80	55	12.12	↑ 4.51%	1,321	51.88	53	8.55	↓ 2.97%

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Figure 2 Incidence Rates of Cervical Cancer, Endometrial Cancer, Ovarian Cancer in United States 1979-2013
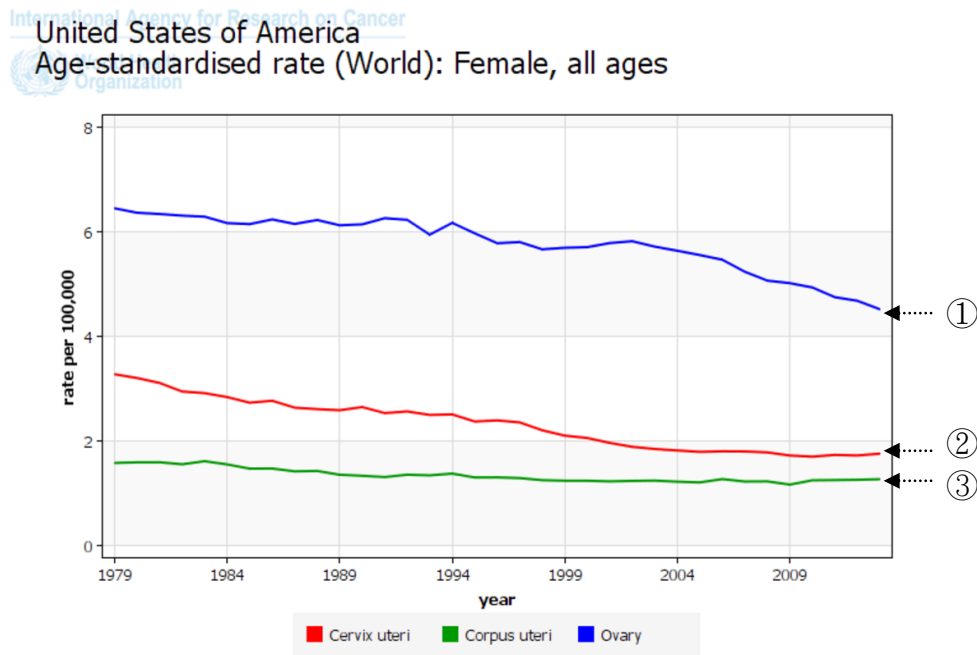
① Ovarian Cancer ② Cervical Cancer ③ Endometrial Cancer
Source: The International Agency for Research on Cancer (IARC), 2016

The risk factors for endometrial cancer include obesity, diabetes, late menopause, unopposed estrogen therapy, and nulliparity (Deligdisch and Holinka, 1987; Grady and Ernster, 1996). Inherited factors have also been suggested as important risk factors for endometrial cancer (Park, 2002). In addition, obesity is one of the well-established risk factors for endometrial cancer. IARC (2002) has shown evidence from both case-control and cohort studies indicating that overweight and obesity are strongly related to the incidence of and the mortality from endometrial cancer. The increase in risk for incidence generally ranges from two to fourth times in overweight or obese women compared to normal weight women, and the increase in risk for death may be slightly higher (Calle et al., 2003).

Since 1980s, obesity has more than doubled globally and is now considered as a major health concern and a global epidemic. According to the World Health Organization (WHO), there were over 1.9 billion overweight adults worldwide with 600 million obese adults in 2014(WHO, 2015). Obesity is a major risk factor for musculoskeletal disorders, type 2 diabetes mellitus, obstructive sleep apnea, cardiovascular disease, and cancers (colorectal, prostate, endometrial, and breast). In Taiwan, based on the data from the Nutrition and Health Survey by the Bureau of Health Promotion (BHP) (https://cris.hpa.gov.tw/pagepub/Home.aspx), in 1996, 33% of the nation's adults were either overweight or obese. In 2008, the number had increased to 44%. The proportion of overweight or obese males rose from 33% to 51%, and the proportion of overweight or obese females went from 33% to 36%. Of the 10 main causes of death in Taiwan in 2011 (Figure 3), eight were related to obesity, including cancer, heart disease, cerebrovascular disease, diabetes, chronic respiratory disease, chronic liver disease and cirrhosis, kidney disease, and hypertension.

Table 2 Statistical Trend of Cervical Cancer, Endometrial Cancer, Ovarian Cancer in United States from 1979-2014

Years	Cervical Cancer		Endometrial Cancer		Ovarian Cancer	
	No. of Deaths	Incidence Rate	No. of Deaths	Incidence Rate	No. of Deaths	Incidence Rate
1979	4935	3.26	2857	1.57	10564	6.44
1980	4873	3.19	2977	1.58	10731	6.35
1981	4815	3.10	3036	1.58	10855	6.33
1982	4630	2.93	3019	1.54	11057	6.30
1983	4651	2.90	3212	1.6	11213	6.28
1984	4564	2.83	3122	1.54	11208	6.15
1985	4508	2.72	3003	1.46	11357	6.13
1986	4557	2.76	3087	1.46	11728	6.22
1987	4423	2.62	3045	1.41	11838	6.14
1988	4443	2.60	3120	1.41	12213	6.21
1989	4487	2.58	2983	1.34	12256	6.11
1990	4627	2.64	3029	1.32	12566	6.13
1991	4514	2.52	2973	1.30	13028	6.25
1992	4641	2.55	3176	1.34	13181	6.22
1993	4582	2.49	3163	1.33	12870	5.93
1994	4602	2.50	3227	1.36	13500	6.16
1995	4503	2.36	3136	1.29	13341	5.96
1996	4540	2.38	3193	1.29	13161	5.77
1997	4499	2.34	3172	1.28	13507	5.79
1998	4340	2.19	3158	1.24	13390	5.65
1999	4204	2.09	3121	1.23	13627	5.68
2000	4200	2.04	3139	1.23	14060	5.69
2001	4092	1.95	3185	1.21	14414	5.77
2002	3952	1.88	3187	1.22	14682	5.81
2003	3919	1.83	3261	1.23	14657	5.7
2004	3850	1.81	3272	1.21	14716	5.63
2005	3924	1.78	3259	1.20	14787	5.54
2006	3976	1.79	3449	1.26	14858	5.45
2007	4021	1.79	3377	1.21	14622	5.22
2008	4008	1.77	3436	1.21	14362	5.05
2009	3913	1.71	3334	1.15	14437	5.01
2010	3939	1.69	3644	1.24	14576	4.92
2011	4092	1.72	3714	1.24	14346	4.74
2012	4074	1.71	3812	1.24	14404	4.67
2013	4217	1.74	3903	1.26	14276	4.51
2014	4458	1.78	4028	1.296	14451	4.63

Source: The International Agency for Research on Cancer (IARC), 2016

Results from the 2011–2014 National Health and Nutrition Examination Survey (NHANES), using measured heights and weights, indicate that an estimated 33.9% of U.S. adults aged 20 and over are overweight, more than one-third (age-adjusted 34.9%, crude 35.1%) of U.S. adults were obese in 2011-2012. Overall, the prevalence of obesity among middle-aged adults aged 40-59 was higher than among younger adults aged 20-39 or older adults aged 60 and over (Figure 4).

Figure 3 Prevalence of obesity, by sex and age group, among adults aged 18 and over: Taiwan, 2007–2011
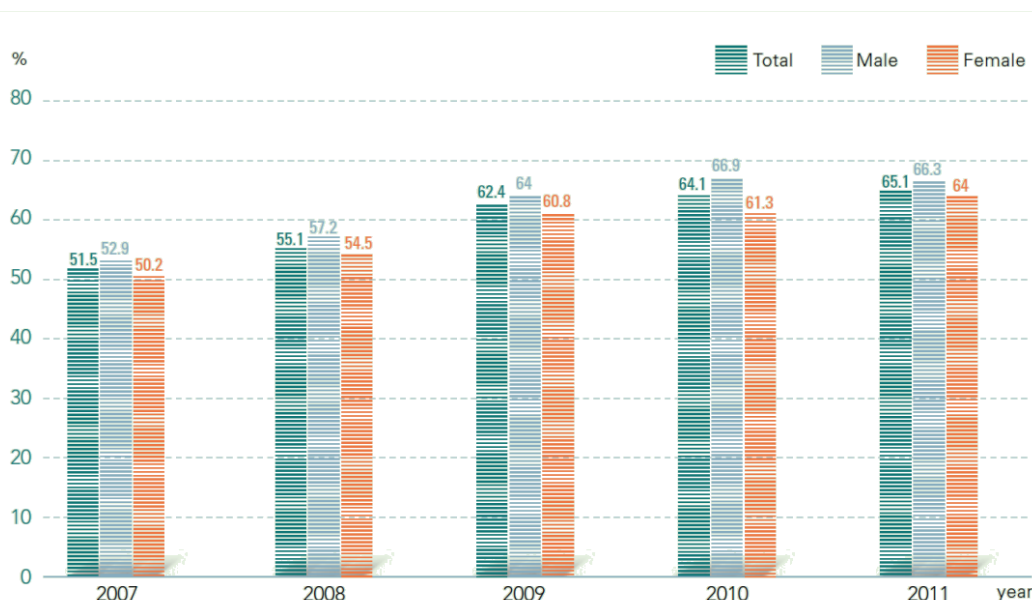
Source: BHP Behavioral Risk Factor Surveillance System (BRFSS) Survey in 2007-2011

Figure 4 Age-adjusted prevalence of obesity, by sex and age group, among adults aged 20 and over: United States, 2011–2012
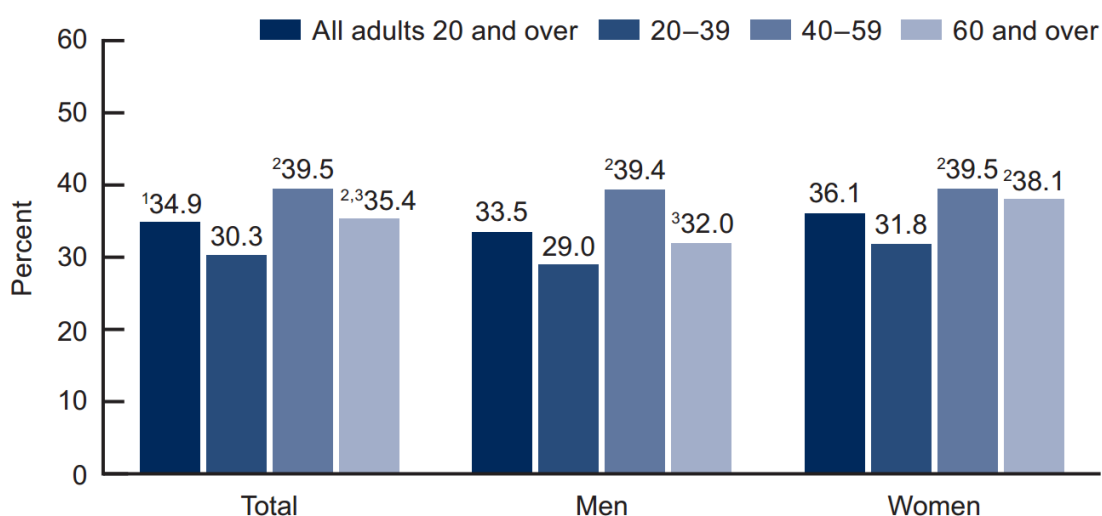
1. Crude estimate 35.1%.

2. Significant difference from ages 20–39.

3. Significant difference from ages 40–59.

NOTE: Estimates are age-adjusted for all adults aged 20 and over by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over.

Source: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2012

Based on the results of Wen et al. (2009), Comparison of relative risks (RR) for mortality from all causes according to BMI level between Taiwan and United States (Figure 5). In Taiwan, RR are adjusted for age, smoking status and gender, with BMI=18.5-24.9 kg/m2 as the reference group; in United States, RR are

adjusted for sex, smoking status, race and alcohol consumption, with BMI=18.5-24.9 kg/m2 as the reference group. For US data, RR at age 60-69 years were from the combined National Health and Nutrition Examination Survey I, II and III and selected from Flegal et al. (2005). The corresponding RR at age 25-59 years were 0.83, 1.20 and 1.83, and at age >= 70 years were 0.91, 1.03 and 1.17, for BMI of 25.0-29.9, 30.0-34.9 and >= 35.0 kg/m2, respectively. In addition, much of the debate was based on the relationship between BMI and morbidity, and rarely on mortality, an important parameter that cannot be ignored in assessing the health impact of obesity.

Figure 5 Comparison of relative risks (RR) for mortality from all causes according to BMI level between Taiwan and United States
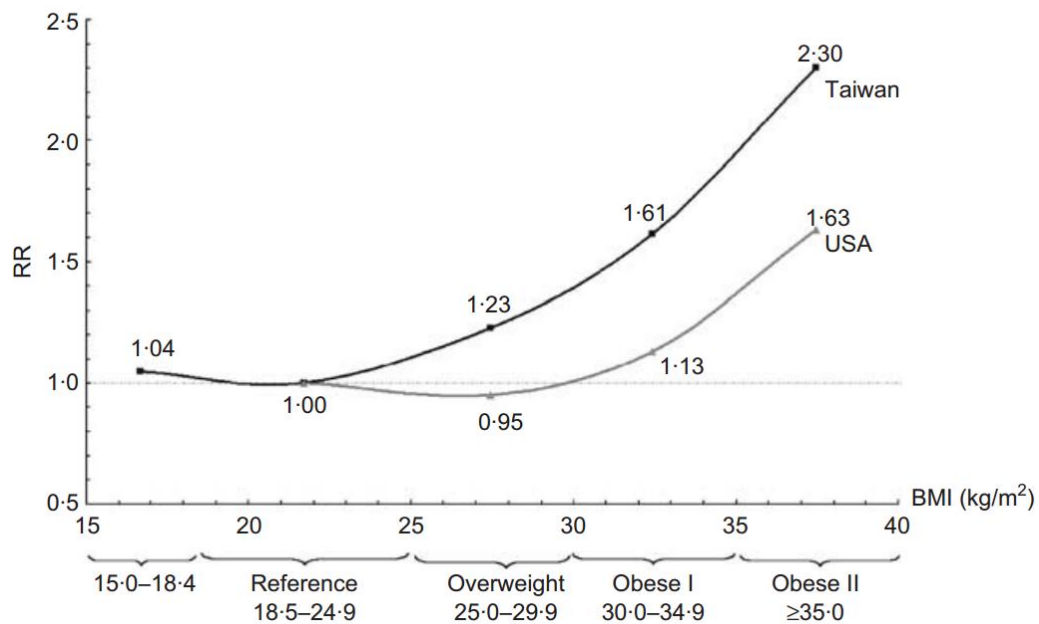
Source: Wen et al (2009). Are Asians at greater mortality risks for being overweight than Caucasians? Redefining obesity for Asians. *Public Health Nutrition* 12(4):497-506.

Factors that influence endometrial cancer survival are of increasing importance as the lifestyle related mortality risk factors for this population may differ from those of the general population. Although being overweight has been established as an important risk factor for endometrial cancer (Bergstrom et al., 2001; Vainio and Bianchini, 2002), it is unclear how obesity and endometrial cancer interplay to affect mortality and life expectancy of adult women. Previous studies focused on body mass index (BMI) and cancer specific mortality among women who were healthy at baseline have reported the strongest association between BMI and endometrial cancer with hazard ratios (HRs) up to 6.25 (95% confidence interval (CI): 3.75–10.42), when comparing women with a BMI $\geqq$ 40 kg/m^2 to those who were normal weight (Calle et al., 2003; Reeves et al., 2007). This magnitude of risk is two times more than the risk for all causes mortality in similar women with a BMI $\geqq$ 40 kg/m^2. Arem and Irwin (2013) identified 12 published studies on obesity and endometrial cancer survival and suggested that elevated BMI at diagnosis was associated with worse survival among endometrial cancer survivors, with death risks ranging from 1.86-2.76 for women with a BMI $\geqq$40 kg/m2

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compared with nonobese women (Modesitt et al., 2007; von Gruenigen et al., 2006). Table 3 has shown that the both standard of Body mass index (BMI), expressed as weight in kilograms divided by height in meters squared (kg/m2). In United States, it is commonly used to classify overweight (BMI 25.0–29.9), obesity (BMI greater than or equal to 30.0), and extreme obesity (BMI greater than or equal to 40.0); In Taiwan, it is commonly used to classify overweight (BMI 24.0–26.9), obesity (BMI greater than or equal to 27.0).

Table 3 The BMI standards of United States and Taiwan

United States	Taiwan	Status
<18.5	<18.5	Underweight
18.5-24.9	18.5-23.9	Normal
25-29.9	24-26.9	Overweight
≥30	≥27	Obese

Few studies have examined life expectancy associated with endometrial cancer (Kwon and Lu, 2008). Our study is the first to consider BMI in the relationship between endometrial cancer and mortality rate as well as life years lost associated with endometrial cancer. Our study plans to use both life years lost and mortality rate, which are accepted outcome measures of population health (Parrish, 2010; Pronk et al., 2013). The goal of this study is to investigate the mortality risks associated with endometrial cancer according to BMI level and to predict life years lost in a general female population in Taiwan. We will use electronic medical record from three medical centers: Chung-Shan Medical University Hospital (CSMUH), Taichung Veterans General Hospital (TVGH), China Medical University Hospital (CMUH) and Washington Univ. in St. Louis (Missouri Baptist Medical Center, MBMC). We will conduct analyses using survival models and compute mortality risk associated with obesity. The projection of life years will be computed based on the mortality estimates and the observed characteristics of the sample as a snapshot of their life span. This approach is not restricted by the length of mortality follow-up and the observed mortality rates, and thus, provides an alternative to the life table approach (Aragon et al., 2008).

2. METHODS

Our project will use the mixed proportional hazard (MPH) model (Lancaster, 1979), which expands on the Cox proportional hazards (PH) model (Cox, 1972). The MPH model is a proportional hazards model with multiplicative unobserved heterogeneity. The importance of accounting for unobserved heterogeneity in the frailty model has been previously studied (Lancaster, 1979; Vaupel et al., 1979; Heckman and Singer; 1984; Abbring and Van den Berg, 2007). It has been noted that individuals with relatively high hazard rates for unobserved reasons die earlier so that samples of survivors are selected. Therefore, the estimated hazard rate of the selected sample increases less fast with duration than that of a random sample. In addition, the estimated partial effects of covariates on the hazard rate of the selected sample are smaller than those on the

hazard rate of a random sample. Consequently, the estimated hazard ratios tend to be biased, and the direction of bias depends on the scale of the down-sized estimates.

Data and the Sample

Data (electronic medical record) from four medical centers: Chung-Shan Medical University Hospital (CSMUH), Taichung Veterans General Hospital (TVGH), China Medical University Hospital (CMUH) and Washington Univ. in St. Louis (Missouri Baptist Medical Center, MBMC) will be used in this project.

The medication records of personal identification number from January 1, 2010 to December 31, 2015 will be analyzed to examine temporal changes. This study will analyze in persons with personal identification number by analyzing data from CSMUH, TVGH, CMUH, MBMC, respectively. Surveillance Survey in Taiwan and United States were conducted from 1995 to 2015. The Sample data files from 2000 to 2015 will be used in three medical centers by personal identification number.

We will only focus on endometrial cancer; therefore, our sample included only women. The sample exclusion criteria will be the following:
(i) individuals with any missing data;
(ii) smoking individuals, because analyses can be confounded by illnesses associated with smoking;
(iii) pregnant women at diagnosis, because BMI levels are unstable during pregnancy;
(iv) individuals reporting any type of cancer other than endometrial cancer to exclude the possibility of endometrial cancer as a secondary cancer; and
(v) underweight women, because disease-driven weight loss could perplex the analysis.

This retrospective study will be reviewed by the Chung Shan Medical University Hospital Medical Institutional Review Board. (Appendix A)

Specifications in the MPH model

Let uppercase letters denote random variables and lowercase letters denote the realizations of the corresponding random variables. Denote θ as the hazard rate, i.e., transition rate to death. For each individual, the hazard rate is determined by the following equation:

$$\theta(t|v, x^{'}, \beta^{'}) = \lambda(t) \cdot v \cdot \exp(x^{'}\beta) \tag{1}$$

where $\lambda(t)$ is the baseline hazard; v is the unobserved heterogeneity, which has the distribution Gamma; β is a vector of parameters to be estimated; and x is a vector of covariates, which consist of an intercept, educational attainment, endometrial cancer, BMI information (BMI classifications, inverted BMI, BMI level, or quadratic form of BMI), alcohol consumption, and physical activities. The outcome variable is age at death,

denoted by T. Further assume that the baseline hazard, $\lambda(t)$, is piecewise constant (Han and Hausman, 1990; Gray, 1994; Yamaguchi et al., 2002). We will normalize $\lambda_1 (\lambda_1 = 1)$. The unobserved heterogeneity, ν, will be assumed to have a gamma distribution based on Abbring and van den Berg's findings (2007): in a large class of hazard models with proportional unobserved heterogeneity, the distribution of the heterogeneity among survivors converges to a gamma distribution. Published studies that assume gamma heterogeneity include Nielsen et al. (1992), Murphy (1994, 1995), Rahgozar et al. (2008), and so on. Further, we will restrict that $E(V) = 1$ for identification purpose (Elbers et al., 1982). Therefore, the gamma distributed V ill have one parameter to be estimated, denoted k, i.e., $V \sim Gamma(k, k)$.

Estimation

We will use maximum likelihood estimation to estimate the parameters in the MPH model. The individual likelihood function, ℓ, derived from equation (1), is shown as follows:

$$\ell(\beta', G, \lambda_2, ..., \lambda_{12} | t, x') = \left\{ \int e^{-\exp(x'\beta)\nu\Lambda(t)} e^{x'\beta} \nu\Lambda'(t) dG(\nu) \right\}^d \cdot \left\{ \int e^{-\exp(x'\beta)\nu\Lambda(t)} e^{x'\beta} dG(\nu) \right\}^{1-d} \tag{2}$$

where $\Lambda(t)$ is the integrated hazard; $\Lambda'(t)$ is the derivative of $\Lambda(t)$ with respect to t; $G(\nu)$ denotes the cumulative distribution function of ν; and d is a binary variable, equal to 1 if the study cohort died before 2011 and 0 otherwise.

Statistical Analysis

A survival model with gamma frailty and gompertz baseline will be used (Vaupel et al., 1979). The estimates will be used to compute hazard ratios for death (relative risks, RRs) (Klein and Moeschberger, 2003) by BMI category (Table 2) for women with endometrial cancer and without any cancer. Life years will be predicted by a closed-form expression (Missov, 2010). The sample will be divided into subsamples with different combinations of age, and obesity status (obese: class I-III and non-obese: normal-weight and overweight individuals). For each subsample, life years are predicted based on the characteristics of the subsample. Within the same subsample, life years lost will be projected by comparing the predicted life years of women with endometrial cancer to the predicted life years of the same women had they not had endometrial cancer. The bootstrap method will be used to resample the subpopulations 1,000 times to compute the means and standard errors (Horowitz, 1994). STATA (13, Stata Corp, College Station, TX) will be used to obtain the summary statistics for the sample and the population, and MATLAB (R2013a, MathWorks Inc, Natick, MA) will be used to perform estimations and predictions.

Outcome Variable and Covariates

The outcome variable is age at death or censor (December 31, 2015). We will control for BMI, age at diagnosis, cancer stage, alcohol consumption, physical activities, and educational attainment.

In Taiwan, BMI classifications are based on the standards established by the Department of Health: Overweight if BMI $\in$ [24, 26.9) kg/m2, class I obese if BMI $\in$ [26.9, 30) kg/m2, class II obese if BMI $\in$ [30, 35) kg/m2, and class III obese if BMI is at least 35 kg/m2. Normal-weight women with BMI $\in$ [18.5, 23.9) kg/m2 are the reference group. In United States, BMI classifications are based on the standards established by the Office of Disease Prevention and Health: Overweight if BMI $\in$ [25, 29.9) kg/m2, class I obese if BMI $\in$ [30, 34.9) kg/m2, class II obese if BMI $\in$ [35, 39.9) kg/m2, and class III obese if BMI is at least 40 kg/m2. Normal-weight women with BMI $\in$ [18.5, 24.9) kg/m2 are the reference group.

Age at diagnosis will be described using eight age categories: 20 to 29, 30 to 39, 40 to 49, 50 to 55, 56 to 75, and age 76 and above. Age < 20 is the reference category. Interaction terms of endometrial cancer status with BMI, and age groups will be included as covariates. The additional covariates are dichotomized as follows: educational attainment (whether an individual was a high school graduate); alcohol consumption; and physical activity (whether an individual engaged in light/modest or vigorous physical activity for at least 10 minutes more than once per day).

5. THE RESULT

In this study, endometrial cancer increased risk of mortality depending on degree of obesity and decreased life years by 1 to 16 years depending on age, and obesity status. Relative risks for death increased with degree of obesity. Obese women under age 55 across both national groups were predicted to lose the most life years; USA group (15.1 y) more than Taiwan group (11.6 y) lost the most life years. The number of life years lost associated with endometrial cancer was more marked for more obese than for less obese women and for women under age 55 and women aged 76 or older than for women aged 56 through 75. Public health promotion should put more emphasis on the prevention and control of obesity for these target populations.

6. DISCUSSION AND CONCLUSION

To our knowledge, our study is the first to consider BMI in the relationship between endometrial cancer and mortality rate as well as life years lost associated with endometrial cancer. In future work, the relationship between obesity and endometrial cancer has been extensively investigated in Taiwanese female population. Recommendations for future research could be: to consider BMI in the relationship between endometrial

cancer and mortality rate as well as life years lost associated with endometrial cancer in a longitudinal study.

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目標達成度：100%

計畫成果：

過去研究針對子宮內膜癌與肥胖的因果關係已經被廣泛的研究並獲得證實；但針對台灣婦女罹患子宮內膜癌風險與肥胖對其死亡率和預期壽命的影響，則尚未得到充分的研究。根據樣本不同身體質量指數(BMI)狀態，分別使用 Gamma Frailty Model 與 Gompertz Baseline 兩種存活模式，分析美國與台灣婦女罹患子宮內膜癌的年齡估計死亡率及其壽命年損失的預測。研究結果顯示，子宮內膜癌根據肥胖程度增加死亡的風險，根據年齡和肥胖狀況將壽命縮短 1 至 16 歲。死亡的相對危險度隨著肥胖程度的增加而增加。兩個國家的 55 歲以下肥胖婦女被預測損失最多生命年；美國組（15.1 歲）比台灣組（11.6 歲）損失最多生命年。與子宮內膜癌相關的生命年數減少對於肥胖多於肥胖少的婦女以及 55 歲以下婦女和 76 歲或 76 歲以上婦女比 56 歲至 75 歲婦女更加明顯。公共衛生促進活動應該更加重視對這些目標人群的肥胖預防和控制。

後續發展：本研究目前已經針對全國癌症登記資料庫進行追溯研究分析。期待透過長時間的觀察與發現，提供政策建議。

計畫執行感言：子宮內膜癌在歐美好發地區，是常見骨盆腔內的婦科癌症。以美國為例，其每年發病例有三萬四千名左右，它的發病數目相當於每年卵巢癌發病例的二倍，子宮頸癌的三倍。在臺灣近年來，子宮內膜癌目前在婦女癌症已經竄升為居於第二位死因，診斷個案數目也逐年上升，對於子宮頸癌與子宮內膜癌的比率由五十年代的 40:1(子宮頸癌：子宮內膜癌)，已在近年來增高為 14:1，故子宮內膜癌病例。此外，過去研究針對子宮內膜癌與肥胖的因果關係已經被廣泛的研究並獲得證實；但針對台灣婦女罹患子宮內膜癌風險與肥胖對其死亡率和預期壽命的影響，是另一項值得深入研究的方向。

科技部補助專題研究計畫出席國際學術會議心得報告

計畫編號	MOST　　　106-2221-E-040-010-		
計畫名稱	肥胖與年齡對於子宮內膜癌死亡率的影響：台灣與美國的差異分析		
出國人員 姓名	張啟昌	服務機構 及職稱	中山醫學大學醫學資訊學系
會議時間	106 年 11 月 24 日 至 106 年 11 月 26 日	會議地點	日本 Okinawa
會議名稱	(中文) (英文) International Conference on Intelligent Informatics and BioMedical Sciences		
發表題目	(中文) (英文)　A hybrid of data mining and ensemble learning forecasting for recurrent ovarian cancer		

一、 參加會議經過

2017 年 International Conference on Intelligent Informatics and BioMedical Sciences 年會在日本 Okinawa 召開。本屆的年會為期 3 天，會議主要是一些 Plenary Sessions，在各個 Workshop 間則是會有許多的 Keynote speech 以及 Panel Discussion，讓世界各國的學者都可以做學術上的交流。個人也第一次參加此國際會議，目標針對現階段進行的卵巢癌復發預後指標的研究議題與各國的研究工作者做互相討論，並獲得許多寶貴的經驗。個人的發表論文題目為 "A hybrid of data mining and ensemble learning forecasting for recurrent ovarian cancer"。

二、 與會心得

這是我第一次出席至 International Conference on Intelligent Informatics and BioMedical Sciences 年會，這一次學術的收穫豐富。值得一提的是，，針對臺灣近年來，卵巢癌個案逐漸增多，可見其未來很可能會超過子宮頸癌的趨勢交流彼此意見，也都認為是另一項值得深入研究的方向。

三、 發表論文全文或摘要

This study applied advanced machine learning techniques and combined with ensemble learning, widely considered as the most successful method to produce objective to an inferential problem of recurrent ovarian cancer. In this study, five machine learning approaches including SVM(support vector machine), C5.0, ELM(extreme learning machine), MARS(Multivariate Adaptive Regression Splines) and RF(Random Forests) were considered to find important risk factors and to predict the recurrence-proneness for ovarian cancer. We use ensemble learning to improve the defect of classification accuracy used normal machine learning: first, selecting important risk factors by ensemble learning, then, using the five machine learning approaches to analyze again. The medical records and pathology were accessible by the Chung Shan Medical University Hospital Tumor Registry. The existing literature on recurrent ovarian cancer reveals that factors include Age, Histology, Grade, Pathologic T, Pathologic N, Pathologic M, Pathologic Stage, The International Federation of Gynecology and Obstetrics (FIGO), Surgical Margins, Performance status, CA125, Operation Optimal Debulking, Chemotherapy Guideline. There are totally 987 patients in the data set. In our study, C5.0 is the superior approach in predicting recurrence of ovarian cancer. Moreover, the classification accuracy of C5.0, MARS, RF and SVM indeed increases after using ensemble learning. Particularly the classification accuracy of C5.0 obviously improves by using ensemble learning with hybrid scheme.

四、 建議

個人建議除了參與在美洲與歐洲會議的機會外，應當可以考慮出席在亞太地區所主辦的各項癌症相關的重要年會。其優點在於亞太地區學術的進步性不會比美洲與歐洲遜色，更重要的是可以與許多重要一學期刊的主編結識，有利於在國際學術地位的發展。

五、 攜回資料名稱及內容

攜回資料名稱及內容（附件：與會手冊封面、論文暨海報發表時程）International Conference on Intelligent Informatics and BioMedical Sciences 年會大會手冊，內容包括研討會宗旨、大會議程、發表之論文摘要等相關資訊。

106年度專題研究計畫成果彙整表

計畫主持人：張啟昌				計畫編號：106-2221-E-040-010-	
計畫名稱：肥胖與年齡對於子宮內膜癌死亡率的影響：台灣與美國的差異分析					

成果項目				量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文		0	篇	
		研討會論文		0		
		專書		0	本	
		專書論文		0	章	
		技術報告		0	篇	
		其他		0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0	
			新型/設計專利	0		
		商標權		0		
		營業秘密		0		
		積體電路電路布局權		0		
		著作權		0		
		品種權		0		
		其他		0		
	技術移轉	件數		0	件	
		收入		0	千元	
國外	學術性論文	期刊論文		0	篇	
		研討會論文		1		出席International Conference on Intelligent Informatics and BioMedical Sciences國際會議，口頭發表一篇
		專書		0	本	
		專書論文		0	章	
		技術報告		0	篇	
		其他		0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	0	
			新型/設計專利	0		
		商標權		0		
		營業秘密		0		
		積體電路電路布局權		0		

		著作權	0		
		品種權	0		
		其他	0		
	技術移轉	件數	0	件	
		收入	0	千元	
參與計畫人力	本國籍	大專生	0	人次	
		碩士生	0		
		博士生	0		
		博士後研究員	0		
		專任助理	0		
	非本國籍	大專生	0		
		碩士生	0		
		博士生	0		
		博士後研究員	0		
		專任助理	0		
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）					

科技部補助專題研究計畫成果自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）或其他有關價值等，作一綜合評估。

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1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估
   ■達成目標
   □未達成目標（請說明，以100字為限）
   　　　□實驗失敗
   　　　□因故實驗中斷
   　　　□其他原因
   說明：

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2. 研究成果在學術期刊發表或申請專利等情形（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊）
   論文：□已發表　□未發表之文稿　■撰寫中　□無
   專利：□已獲得　□申請中　■無
   技轉：□已技轉　□洽談中　■無
   其他：（以200字為限）
   本研究目前已經針對全國癌症登記資料庫進行追溯研究分析。期待透過長時間的觀察與發現，提供後續論文發表與政策建議。

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3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性，以500字為限）
   本研究計畫結果顯示，子宮內膜癌根據肥胖程度增加死亡的風險，根據年齡和肥胖狀況將壽命縮短1至16歲。死亡的相對危險度隨著肥胖程度的增加而增加。兩個國家的55歲以下肥胖婦女被預測損失最多生命年；美國組（15.1歲）比台灣組（11.6歲）損失最多生命年。與子宮內膜癌相關的生命年數減少對於肥胖多於肥胖少的婦女以及55歲以下婦女和76歲或76歲以上婦女比56歲至75歲婦女更加明顯。公共衛生促進活動應該更加重視對這些目標人群的肥胖預防和控制。子宮內膜癌在歐美好發地區，是常見骨盆腔內的婦科癌症。以美國為例，其每年發病例有三萬四千名左右，它的發病數目相當於每年卵巢癌發病例的二倍，子宮頸癌的三倍。在臺灣近年來，子宮內膜癌目前在婦女癌症已經竄升為居於第二位死因，診斷個案數目也逐年上升，對於子宮頸癌與子宮內膜癌的比率由五十年代的40:1(子宮頸癌：子宮內膜癌)，已在近年來增高為14:1，故子宮內膜癌病例。此外，過去研究針對子宮內膜癌與肥胖的因果關係已經被廣泛的研究並獲得證實；但針對台灣婦女罹患子宮內膜癌風險與肥胖對其死亡率和預期壽命的影響，是另一項值得深入研究的方向。

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4. 主要發現

本研究具有政策應用參考價值：■否　□是，建議提供機關

（勾選「是」者，請列舉建議可提供施政參考之業務主管機關）

本研究具影響公共利益之重大發現：□否　□是

說明：（以150字為限）

期待透過長時間的觀察與發現，提供政策建議。