科技部補助專題研究計畫成果報告
期末報告

雌激素與子宮頸癌等女性賀爾蒙依賴性癌症發生的關係：健康資料串聯研究與臨床前期研究

計 畫 類 別 ： 個別型計畫
計 畫 編 號 ： NSC 102-2629-B-303-001-
執 行 期 間 ： 102 年 08 月 01 日至 103 年 07 月 31 日
執 行 單 位 ： 佛教慈濟醫療財團法人花蓮慈濟醫院婦產部

計 畫 主 持 人 ： 朱堂元
共 同 主 持 人 ： 陳祈安、謝佳容
計畫參與人員： 學士級-專任助理人員：石宴禎

處 理 方 式 ：
1.公開資訊：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢
2.「本研究」是否已有嚴重損及公共利益之發現：否
3.「本報告」是否建議提供政府單位施政參考：否

中 華 民 國 103 年 10 月 30 日

中 文 摘 要 ： 背景：女性子宮頸癌的成因除了人類乳突病毒（HPV）的感染與癌化之外，第二個重要的關鍵是雌激素。大型流行病學研究顯示子宮頸癌的發生與雌激素的長期刺激有密切關係。HPV E7 基因轉殖小鼠的研究顯示，雌激素及其受體 ERα 是子宮頸癌化過程中全程參且必要之因素，雌激素受體拮抗劑（SERMs）不但可預防癌病變的發生，且可逆轉已經發生之癌前病變及侵犯性癌，以致完全治癒。初期的臨床觀察也顯示 Tamoxifen 對復發子宮頸癌有一定之療效。這顯示雌激素在子宮頸癌的角色與重要性明顯被低估。方法：本研究所要探討的問題為：使用雌激素受體拮抗劑是否能預防乳癌婦女的子宮頸癌的發生？本研究以「衛生署健康資料加值應用協作中心」提供之 1998-2008 年之資料作串連分析研究，包括癌症登記檔建、全民健保學術研究資料庫之承保資料檔(ID)、門診處方及治療明細檔(CD)、門診處方醫令明細檔(OO)、住院醫療費用醫令清單明細檔(DO)與住院醫療費用清單明細檔(DD)等。其中抗雌激素使用之累積日數(cDDD) 為 88(418-1531)天，超過 90%的使用者在治療期間有 50%以上之醫囑遵循率。我們已 Cox regression 分析比較用藥組與未用藥組間子宮頸病變之發生情形，並調整年齡、子宮頸抹片情形以及化學治療等因素。結果： 在為期 11 年的追蹤中，子宮頸上皮低度病變（LSIL）、高度病變（HSIL)、原位癌（CIS)及侵犯性癌（ICC）在用藥組與未用藥組的發生比率（95%信賴區間）分別個為每十萬人 182・3（162・0-205・1）vs. 257・8（219・3-303・0), 52・4（42・0-65・3）vs. 74・0（54・7-100・1), 72・2（59・9-87・2）vs. 74・0（54・7-100・1）及 35・1（26・9-46・0）vs. 42・3（28・3-63・1)。使用抗雌激素者之 LSIL 及 HSIL 的發生率明顯為低，調整後之風險比分別為 0.60（0.40-0.63)及 0.65（0.44-0.95)； 此一現象在每兩年至少有做一次抹片的族群更為明顯，風險比分別為 182・3（162・0-205・1）vs. 257・8（219・3-303・0), 52・4（42・0-65・3）vs. 74・0（54・7-100・1), 72・2（59・9-87・2）vs. 74・0（54・7-100・1）and 35・1（26・9-46・0）vs. 42・3（28・3-63・1)。在診斷乳癌後有接受過化學治療的族群的這四種子宮頸腫瘤的發生風險比還要更為降低，分別是 0・46（0・35-0・59), 0・48（0・29-0・81), 0・63（0・40-0・99）及 0・52（0・27-0・97)。此一保護效果符合子宮頸腫瘤的發展，亦即對 LSI1 的保護在追蹤不久後即出現，HSIL 的保護在追蹤 2 年後出現，ICC 的保護則直到第 7 年才出現。結論；使用抗雌激素藥物可以明顯減少子宮頸癌及癌前病變之發生，此結果顯示子宮頸癌的發生需要雌激素的作

用。

中文關鍵詞： 雌激素、子宮頸癌、子宮頸癌前病變、抗雌激素治療

英文摘要： Background: Estrogen has been proven to be a necessity for cervical carcinogenesis by transgenic studies, but its role in human cervical carcinogenesis remains unclear.
Methods: Breast cancer patients with and without long-term antiestrogen therapy were identified from the Taiwan National Health Insurance Database between 1998 and 2008. Antiestrogens were used with a median cumulative defined daily dose (IQR) of 886 (418-1531). Over 90% of the users adhered to antiestrogen for more than 50% of the therapeutic duration. The risk of cervical neoplasia was compared between antiestrogen users and nonusers with Cox regression analysis, and adjusted for age, Pap smear density and chemotherapy.Findings: During the 11-year follow-up, the incidences per 100000 person years (95% CI) of low-grade dysplasia, high-grade dysplasia, carcinoma in situ and invasive cervical cancer (ICC) between antiestrogen users and nonusers were 182·3 (162·0-205·1) vs. 257·8 (219·3-303·0), 52·4 (42·0-65·3) vs. 74·0 (54·7-100·1), 72·2 (59·9-87·2) vs. 74·0 (54·7-100·1) and 35·1 (26·9-46·0) vs. 42·3 (28·3-63·1), respectively. Use of antiestrogen conferred a significant lower risk for low-grade dysplasia and high-grade dysplasia [adjusted HR (95% CI) of 0·60 (0·49-0·74) and 0·65 (0·44-0·95), respectively], and still lower one in patients with Pap smear every two year [adjusted HR of 0·50 (0·40-0·63) and 0·51 (0·31-0·83), respectively]. In patients who received chemotherapy, assumed to have eliminated pre-existing cervical lesions, adjusted HRs for the four types of cervical neoplasia reduced to 0·46 (0·35-0·59), 0·48 (0·29-0·81), 0·63 (0·40-0·99) and 0·52 (0·27-0·97), respectively. In contrast to an early divergence of cumulative incidence of low-grade dysplasia between users and nonusers, the divergence of high-grade dysplasia and ICC occurs and becomes significant at later years of follow-up.

Interpretation: Antiestrogen use reduced the incidences of cervical neoplasia in this breast cancer cohort. The results demonstrate the estrogen dependence of cervical neoplasia in humans.

英文關鍵詞： cervical cancer, cervical intraepithelial neoplasm, antiestrogen

附件一

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）

（計畫名稱）

雌激素與子宮頸癌等女性賀爾蒙依賴性癌症發生的關係:健康資料串聯研究與臨床前期研究

計畫類別：■個別型計畫　□整合型計畫
計畫編號：NSC 102-2629-B-303-001
執行期間： 102 年 08 月 01 日～ 103 年 07 月 31 日

執行機構及系所：花蓮慈濟醫院

計畫主持人：朱堂元
共同主持人：陳祈安教授(醫學院婦產科)、謝佳容助理教授(公共衛生學系)
計畫參與人員：石宴禎專任助理

本計畫除繳交成果報告外，另含下列出國報告，共 0 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

期末報告處理方式：
1. 公開方式：
   □非列管計畫亦不具下列情形，立即公開查詢
   □涉及專利或其他智慧財產權，□一年■二年後可公開查詢
2.「本研究」是否已有嚴重損及公共利益之發現：■否 □是
3.「本報告」是否建議提供政府單位施政參考 ■否 □是，____（請列舉提供之單位；本部不經審議，依勾選逕予轉送）

中　華　民　國 103 年 10 月 31 日

科技部補助專題研究計畫成果報告自評表

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（簡要敘述成果是否有嚴重損及公共利益之發現）或其他有關價值等，作一綜合評估。

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：

2. 研究成果在學術期刊發表或申請專利等情形：

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 100 字為限）

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），如已有嚴重損及公共利益之發現，請簡述可能損及之相關程度（以 500 字為限）

本研究以健保資料庫重大傷病檔做乳癌病人為研究世代，研究抗雌激素治療對子宮頸癌及癌前期病變之發生之影響，發現長期使用抗雌激素藥物可以明顯減少子宮頸癌及癌前病變之發生。研究結果之影響價值有下：

（一） 學術上，率先發現抗雌激素有預防子宮頸癌的效果。提出全人口群的長期追蹤的研究證據。並首度從人身上證實雌激素為子宮頸癌生成的第二元兇，證實了基因轉殖小鼠研究所發現之雌激素及雌激素受體為人類乳突病毒導致子宮頸癌化的必要關鍵。小鼠研究發現之抗雌激素藥物對子宮頸癌有治療效果，在此人群研究中也得到間接之佐證。

（二） 本研究提供以抗雌激素藥物作為子宮頸癌高危險族群（如 HPV 病毒持續感染者，子宮頸上皮低度病變者）化學預防的基礎。

（三） 本研究之結果強力支持，PI 目前執行中之 NRPB 臨床試驗計畫：「Tamoxifen 與 Letrozole 在復發或持續性子宮頸鱗狀上皮癌之療效及新生物標記：多中心、隨機分配二期臨床試驗」。

一、　中、英文摘要及關鍵詞（keywords）。

（一）　中文摘要：

背景：女性子宮頸癌的成因除了人類乳突病毒（HPV）的感染與癌化之外，第二個重要的關鍵是雌激素。大型流行病學研究顯示子宮頸癌的發生與雌激素的長期刺激有密切關係。HPV E7 基因轉殖小鼠的研究顯示，雌激素及其受體 ERα 是子宮頸癌化過程中全程參且必要之因素，雌激素受體拮抗劑（SERMs）不但可預防癌病變的發生，且可逆轉已經發生之癌前病變及侵犯性癌，以致完全治癒。初期的臨床觀察也顯示 Tamoxifen 對復發子宮頸癌有一定之療效。這顯示雌激素在子宮頸癌的角色與重要性明顯被低估。

方法：本研究所要探討的問題為：使用雌激素受體拮抗劑是否能預防乳癌婦女的子宮頸癌的發生？本研究以「衛生署健康資料加值應用協作中心」提供之 1998-2008 年之資料作串連分析研究，包括癌症登記檔建、全民健保學術研究資料庫之承保資料檔(ID)、門診處方及治療明細檔(CD)、門診處方醫令明細檔(OO)、住院醫療費用醫令清單明細檔(DO)與住院醫療費用清單明細檔(DD)等。其中抗雌激素使用之累積日數(cDDD) 為 88(418-1531)天，超過 90％的使用者在治療期間有 50％以上之醫囑遵循率。我們已 Cox regression 分析比較用藥組與未用藥組間子宮頸病變之發生情形，並調整年齡、子宮頸抹片情形以及化學治療等因素。

結果： 在為期 11 年的追蹤中，子宮頸上皮低度病變（LSIL）、高度病變 (HSIL)、原位癌 (CIS) 及侵犯性癌 (ICC) 在用藥組與未用藥組的發生比率 (95%信賴區間) 分別個為每十萬人 182·3 (162·0-205·1) vs. 257·8 (219·3-303·0), 52·4 (42·0-65·3) vs. 74·0 (54·7-100·1), 72·2 (59·9-87·2) vs. 74·0 (54·7-100·1) 及 35·1 (26·9-46·0) vs. 42·3 (28·3-63·1)。使用抗雌激素者之 LSIL 及 HSIL 的發生率明顯為低，調整後之風險比分別為 0.60 (0.40-0.63) 及 0.65 (0.44-0.95); 此一現象在每兩年至少有做一次抹片的族群更為明顯，風險比分別為 182·3 (162·0-205·1) vs. 257·8 (219·3-303·0), 52·4 (42·0-65·3) vs. 74·0 (54·7-100·1), 72·2 (59·9-87·2) vs. 74·0 (54·7-100·1) and 35·1 (26·9-46·0) vs. 42·3 (28·3-63·1)。在診斷乳癌後有接受過化學治療的族群的這四種子宮頸腫瘤的發生風險比還要更為降低，分別是 0·46 (0·35-0·59), 0·48 (0·29-0·81), 0·63 (0·40-0·99) 及 0·52 (0·27-0·97)。此一保護效果符合子宮頸腫瘤的發展，亦即對 LSIl 的保護在追蹤不久後即出現，HSIL 的保護在追蹤 2 年後出現，ICC 的保護則直到第 7 年才出現。

結論；使用抗雌激素藥物可以明顯減少子宮頸癌及癌前病變之發生，此結果顯示子宮頸癌的發生需要雌激素的作用。

關鍵詞：雌激素、子宮頸癌、子宮頸癌前病變、抗雌激素治療

(二)英文摘要：

Background: Estrogen has been proven to be a necessity for cervical carcinogenesis by transgenic studies, but its role in human cervical carcinogenesis remains unclear.

Methods: Breast cancer patients with and without long-term antiestrogen therapy were identified from the Taiwan National Health Insurance Database between 1998 and 2008. Antiestrogens were used with a median cumulative defined daily dose (IQR) of 886 (418-1531). Over 90% of the users adhered to antiestrogen for more than 50% of the therapeutic duration. The risk of cervical neoplasia was compared between antiestrogen users and nonusers with Cox regression analysis, and adjusted for age, Pap smear density and chemotherapy.

Findings: During the 11-year follow-up, the incidences per 100000 person years (95% CI) of low-grade dysplasia, high-grade dysplasia, carcinoma in situ and invasive cervical cancer (ICC) between antiestrogen users and nonusers were 182·3 (162·0-205·1) vs. 257·8 (219·3-303·0), 52·4 (42·0-65·3) vs. 74·0 (54·7-100·1), 72·2 (59·9-87·2) vs. 74·0 (54·7-100·1) and 35·1 (26·9-46·0) vs. 42·3 (28·3-63·1), respectively. Use of antiestrogen conferred a significant lower risk for low-grade dysplasia and high-grade dysplasia [adjusted HR (95% CI) of 0·60 (0·49-0·74) and 0·65 (0·44-0·95), respectively], and still lower one in patients with Pap smear every two year [adjusted HR of 0·50 (0·40-0·63) and 0·51 (0·31-0·83), respectively]. In patients who received chemotherapy, assumed to have eliminated pre-existing cervical lesions, adjusted HRs for the four types of cervical neoplasia reduced to 0·46 (0·35-0·59), 0·48 (0·29-0·81), 0·63 (0·40-0·99) and 0·52 (0·27-0·97), respectively. In contrast to an early divergence of cumulative incidence of low-grade dysplasia between users and nonusers, the divergence of high-grade dysplasia and ICC occurs and becomes significant at later years of follow-up.

Interpretation: Antiestrogen use reduced the incidences of cervical neoplasia in this breast cancer cohort. The results demonstrate the estrogen dependence of cervical neoplasia in humans.

Key words: cervical cancer, cervical intraepithelial neoplasm, antiestrogen

二、 報告內容：包括前言、研究目的、文獻探討、研究方法、結果與討論（含結論與建議）等。

Introduction

As the second most common malignancy in women worldwide, cervical cancer is the leading cause of cancer death in developing countries that lack organized Pap smear screening.[1] Although human papillomavirus (HPV) is regarded as a necessary etiologic factor in cervical carcinogenesis,[2] only a small fraction of HPV-infected women eventually develop invasive cervical cancer (ICC),[3] implying the presence of other key factors.

Epidemiologic studies have identified long-term hormone exposure that which occurs with high parity and oral contraceptive use, as an independent risk factor for ICC.[4, 5] In unscreened populations, the incidence of ICC in women increases coincidently with aging after reproductive age, then plateaus at menopause and declines at postmenopause.[6] The K14-HPV E6/ E7 transgenic mouse model demonstrated an absolute requirement for estrogen and the estrogen receptor alpha in cervical carcinogenesis.[7] Cervical neoplasia of differing severities developed only when administering 17β-estradiol at physiological levels, with intact ovaries, and with the wild type Esr1 gene.[8] Importantly, removing the estrogen prevented cervical neoplasia or ICC, while administering a selective estrogen receptor modulator (SERM) led to regression of pre-existing cervical neoplasia.[9] However, the role of estrogen in human cervical carcinogenesis remains unclear.

As antiestrogens, SERMs and aromatase inhibitors (AIs) have been prescribed for more than two decades as adjuvant hormone therapy for estrogen receptor positive and/or progesterone receptor positive breast cancer. We conducted a population-based cohort to determine whether antiestrogen use is associated with a lower risk of cervical neoplasia in breast cancer patients.

Methods

Study population and study design

The Taiwan National Health Insurance (NHI) claims database includes comprehensive disease diagnoses, hospital admissions, outpatient visits and prescription medications for 99% of the 23 million inhabitants of Taiwan beginning in 1997. Data for this study were obtained from the Registry for Catastrophic Illness Patient Database (RCIPD), a subset of the Taiwan National Health Insurance (NHI) database, which contains complete medical records of all cancer patients. With the registry of catastrophic illness, cancer patients can receive medical care nearly free of charge while under NHI coverage. These databases have been used previously for epidemiologic research, and the information on diagnoses, prescription medications and hospitalizations is of reliable quality.[10] Women who were diagnosed with breast cancer and registered with the RCIPD from January 1, 1998, to December 31, 2008, were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes of 174.0-174.9 or A code of A113. Figure 1 shows the study design, exclusion criteria and the status of antiestrogens use in the study population. We excluded patients who were male or younger than 18 years old, and those with a history of cervical dysplasia, cervical carcinoma *in situ* (CIS), ICC, hysterectomy, cervical amputation, cervical conization or other cancers

before or at the date of breast cancer diagnosis. While considering the need of long-term follow-up for the incidence of cervical cancer, we also excluded breast cancer patients with lymph node or distant metastasis. Additionally, we excluded those patients whose antiestrogen use was less than 90 cumulative defined daily dose (cDDD) or whose follow-up period was less than 90 days.

The identification of ICC was based on a new registration of ICC in the RCIPD or by the diagnosis of ICC during hospitalization using ICD-9-CM codes of 180·0-180·9 or A code of A120. Cervical CIS (ICD-9-CM 233·1) and cervical dysplasia (ICD-9-CM 622·1) were identified using the relevant ICD-9-CM codes either from hospitalization or from three outpatient visits that accompanied the procedures of conization, cervical biopsy, or endocervical curettage. Cases of cervical dysplasia were considered as high-grade dysplasia when accompanying with cervical conization, and low-grade dysplasia when accompanying with cervical biopsy or endocervical curettage. All patients were followed from the diagnosis of breast cancer to the occurrence of the most severe form of cervical neoplasia. Events that occurred within three months of follow-up were excluded from this study. If no event occurred during follow-up, the patient was followed until death or the end of the cohort.

The antiestrogens covered by the NHI during the study period for breast cancer adjuvant therapy included three SERMs, tamoxifen, raloxifen, and toremifene, and four AIs, anastrozole, letrozole, aminoglutethimide, and exemestane. Additionally, cDDD was calculated to standardize the antiestrogen use across multiple drug types between groups. To demonstrate compliance with and consistency of antiestrogen use, adherence was calculated by dividing the cDDD by the period of prescription.

We explored several risk factors including age,[6] Pap smear density,[11] chemotherapy treatment[12], and drug adherence[13] that might interfere with the association between antiestrogen use and risk of cervical neoplasia. Both the frequency and regularity of Pap smear were of concern. Pap smear density was calculated as the number of Pap smears divided by the number of person-years. Patients with different Pap smear densities were stratified for analysis. The confounders of age and chemotherapy treatment were also controlled. This study was approved by the Research Ethics Committee of Buddhist Tzu Chi General Hospital, Hualien, Taiwan.

Statistical analysis

Demographics and clinical characteristics were described in the median, interquartile range (IQR) and percentage. Data are expressed as median (IQR) or number (percentage). Base on Cox proportional hazards model the hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) were computed, while adjusting for age at the time of breast cancer diagnosis, Pap smear density and chemotherapy treatment. The consistency and difference of risk of cervical neoplasia were evaluated by conducting subgroup analysis for age, chemotherapy, Pap smear density, and antiestrogen adherence. The cumulative incidence of cervical neoplasia adjusted for age, Pap smear density, and chemotherapy treatment, was plotted using the adjusted Kaplan-Meier method.[14] In Taiwan, although occurrence of cervical dysplasia is always identified by Pap screening, ICC is not. In contrast to a 74·9% two-year screening rate in the low-grade dysplasia group, only 31·2% of women with ICC had regular Pap smear screening in this cohort (Webtable 1). Therefore, the adjusted cumulative incidence of cervical dysplasia was analyzed in the subgroup of patients who had Pap smear every two years, and that of CIS or ICC was analyzed in the whole study population. A two-tailed test at a level of 0·05 was considered statistically significant. Statistical analyses were performed using SAS, version 9·3 (SAS, Inc., Cary, NC)

Results

We identified 70368 potentially eligible breast cancer patients who registered for the first time in the RCIPD (Figure 1). After the exclusion criteria were applied, 44949 patients were enrolled in the study. The study consisted of 30939 (68·8%) antiestrogen users and 14010 (31·2%) nonusers. Ninety-five percent of the antiestrogen users had used tamoxifen, while aromatase inhibitor is the next most common use antiestrogen (Figure 1, Table 1). The demographic characteristics of this cohort are shown in Table 1. The median (IQR) follow-up time for the antiestrogen users and nonusers was 4·46 (2·36-7·36) years and 3·44 (1·40-6·42) years, respectively. The antiestrogen users had a higher Pap smear density of 0·39 (0·00-0·80) than 0·12 (0·00-0·60) for the nonusers. The median (IQR) cDDD of antiestrogens was 886 (418-1531). The vast majority (23692, 76.5%) had the medication started within six months of enrollment (Table 1) and had an adherence higher than 0·5 cDDD daily (27920, 90·2%).

After adjusting for age, Pap smear density, and chemotherapy treatment, antiestrogen users had a significantly lower risk of low-grade dysplasia and high-grade dysplasia than nonusers, with an adjusted HR of 0·60 (95% CI, 0·49-0·74) and 0·65 (95% CI, 0·44 to 0·95), respectively (Table 2). According to the subgroup analysis in Table 3, patients who had received chemotherapy had a greater protective effect from antiestrogen use than those who did not receive chemotherapy. The adjusted HRs for low-grade dysplasia, high-grade dysplasia, CIS, and ICC were 0·46 (95% CI, 0·35-0·59), 0·48 (95% CI, 0·29-0·81), 0·63 (95% CI, 0·40-0·99) and 0·52 (95% CI, 0·27-0·97), respectively. Compared to premenopausal patients (18-49 years old), a more pronounced protective effect of antiestrogen use for high-grade dysplasia and CIS was also found in menopausal patients, with adjusted HR of 0·50 (95% CI, 0·27-0·94) and 0·56 (95% CI, 0·32-0·99), respectively. The risk for cervical low-grade dysplasia and high-grade dysplasia was significantly lower in antiestrogen users who ever had a Pap smear compared to whose never had a Pap smear, with adjusted HRs 0·55 (95% CI,0·44-0·68) and 0·62 (95% CI,0·41-0·94), respectively. For those taking a Pap smear every two years, the adjusted HRs for low-grade dysplasia and high-grade dysplasia decreased to 0·50 (95% CI, 0·40-0·63) and 0·51 (95% CI, 0·31-0·83), respectively. In the subgroup of menopausal patients and who had received chemotherapy, the adjusted HRs for low-grade dysplasia, high-grade dysplasia, and CIS further decreased to 0·45 (95% CI, 0·26-0·77), 0·23 (95% CI, 0·09-0·55) and 0·41 (95% CI, 0·20-0·86), respectively.

A lower incidence of differing cervical neoplasia appeared at different follow-up periods. For instance, although low-grade dysplasia occurred as early as five months of follow-up (adjusted HR, 0·36; 95% CI, 0·17-0·75), high-grade dysplasia did not occur until three years of follow-up (adjusted HR, 0·51; 95% CI, 0·31-0·86) (Table 4). In the subanalysis of excluding events occurred within the first seven years, the adjusted HR of ICC in antiestrogen users was 0·19 (95% CI, 0·06-0·62). Figure 2 shows the adjusted Kaplan-Meier curves for cumulative incidence of differing cervical neoplasia. As mentioned earlier, the divergence of cumulative incidences for low-grade dysplasia between the antiestrogen users and nonusers occurred early in follow-up, whereas the divergence for high grade dysplasia and ICC was not apparent until the third and eighth year of follow-up, respectively. Meanwhile, the protective effect of antiestrogen use for low-grade dysplasia was consistently found in the subgroup analysis of SERM-only users versus non-antiestrogen users (Webtable 2). This protective effect was also evident for high-grade dysplasia in the subgroup with Pap smear every two year. A significantly lower risk of ICC was also found in SERMs-only users than non-antiestrogen users when the adherence equal to or higher than 0·5

cDDD (adjusted HR, 0·58; 95% CI, 0·33-0·99).

Discussion

To our knowledge, this is the first population-based study to demonstrate that antiestrogen use is associated with a lower risk of cervical neoplasia in breast cancer patients (panel). This study although followed passively by data linkage, is approaching a population-based cohort with some strengths. First, this naturally occurring cohort is devoid of selection or recall bias. Second, the antiestrogen use is based on an expression of estrogen receptor and/or progesterone receptor in the breast tumor, which is independent on the systemic health status of a patient or the occurrence of cervical neoplasia. Third, according to clinical guidelines, antiestrogens were used immediately after completion of primary therapy [the median (IQR) time to first antiestrogen use was 46 (11-175) days] and were used for a long period of up to five years. Fourth, because the antiestrogen is essential to prevent the recurrence of breast cancer and has minimal side effects, an excellent compliance and adherence were achieved. Over 90% of antiestrogen users had an adherence equal to or more than 0·5 cDDD per day. Fifth, the main tool of the outcomes, Pap smear, is sensitive enough in this population (see discussion below) and 87·4% of the study population received Pap smear during follow-up (Webtable 1). Finally, the 11 year follow-up period was sufficient to identify most of the occurrences of non-invasive cervical neoplasia.

In Taiwan, an organized screening program was initiated three years before this study was performed.[15] A 3-year screening rate increased from 14·5% in 1995 to 60·8% in 2012.[15] In a population-based analysis in Taiwan, the Pap smear sensitivity and specificity for high-grade squamous intraepithelial lesion or more severe diseases were 81·9% and 98·6%, respectively.[16] In the subgroup of patients with a Pap smear every two years, lower adjusted HRs were observed for low-grade and high-grade cervical dysplasia compared to the main model of this study (Table 3). Meanwhile, nonusers of antiestrogen were much less frequently screened than the users [Pap smear density of 0·12 (IQR, 0·0-0·60) vs. 0·39 (IQR, 0·0-0·80) times per year], and a lower incidence of cervical dysplasia should be expected. However, on the contrary we observed a significantly higher incidence of low-grade cervical dysplasia in the antiestrogen nonusers than users before adjusting for Pap smear density. Therefore, the effect of antiestrogen in reducing the incidence of cervical dysplasia is underestimated. Healthcare guidelines in Taiwan recommend to performed a colposcopy when a Pap smear shows an abnormality such as atypical squamous cells of undetermined significance or above. However, approximately 32% of the colposcopy results may be false negative.[17] Therefore, the actual difference in the incidence of cervical neoplasia may be greater than originally estimated. Additionally, the antiestrogen nonuser group has a higher mortality rate than the user group does (11·3% vs. 10·7%). This difference explains the shorter median time of follow-up in the nonuser group [3·44 (IQR, 1·40-6·42) years] than in the user group [4·46 (IQR, 2·36- 7·36) years]. More events should occur if the nonusers were followed as long as the users. Therefore, this study underestimated the reduction in the risk of cervical neoplasia by antiestrogen use.

Approximately 60% of both antiestrogen users and nonusers in the breast cancer cohort received chemotherapy before the administration of antiestrogens. Chemotherapy regimens that are used to treat breast cancer (i.e. paclitaxel, cisplatin, and carboplatin), are also effective for cervical cancer.[12] Thus, patients who received chemotherapy may also have eliminated pre-existing cervical neoplasia that could not be excluded in this retrospective study. During the analysis of this population, the protective effects

of antiestrogens became more prominent in cervical neoplasia of differing severities (Table 3), further supporting the preventive effect of antiestrogens on cervical neoplasia.

The same protection on cervical neoplasia was also evident in the subgroup analysis of the SERM-only users versus non-antiestrogen users. However, the protection, especially for high-grade dysplasia and CIS, was somewhat weaker than that we found in the subgroup analysis of the whole cohort in which AIs was used in 27.2% of users. Interestingly, compared to the younger patients, the protection effect of antiestrogens for these two neoplasia was higher in menopausal patients in whom 33.9% had used AIs (Table 3). Owing to the limited number of patient taking AI-only (1388, 16·5%) in the antiestrogen users, whether AI, as in the case of used in breast cancer,[18] is more effective than SERM in protection from cervical neoplasia warrants further study in future research.

Reduction in the cumulative incidences of differing cervical neoplasia in this study correlates with the natural history of cervical carcinogenesis. In low-grade dysplasia, the protective effect occurred as early as five months of follow-up, suggesting that estrogen is required for the initiation of cervical transformation caused by HPV. This finding echoes to the study of K14HPV E6/E7 transgenic mouse model in which estrogen dependence was found in the earliest lesion of cervical transformation including atypical squamous metaplasia and mild dysplasia.[19] On the other hand, the reduction in the incidence of high-grade dysplasia was not obvious until the third year and that of ICC until the eighth year of follow-up. This observation is, however, still much earlier than the expected at least 6 and 15 years for the development of high-grade dysplasia and ICC, respectively.[20] This discrepancy could be attributed to prevention of pre-existing cervical dysplasia from progression to high-grade dysplasia or ICC in the user group. Another possibility is the therapeutic effect of antiestrogen on cervical neoplasia, as was found in the transgenic mouse model in which administering SERMs to the tumor-bearing transgenic mice cleared the lesions efficiently.[7, 9]

This cohort study has certain limitations. First, this study lacks information regarding important confounders of cervical cancer, including the status of HPV infection,[3] smoking[21] , and endogenous or exogenous hormone exposure (e.g. menopause,[6] parity[4], and oral contraceptives pill[5] use). Menopausal status is unlikely to be a bias because patient of premenopausal (18-49 years old) or menopausal age were nearly equal between the the users and nonusers (49·6% vs. 50·4%). Although about 68% of the breast cancer patients would become amenorrhea after adjuvant chemotherapy,[22] some are reversible. In addition, the percentages of patients receiving chemotherapy in the two groups were approximately the same (61·7% vs. 63·1%). The effect of smoking on the incidence of cervical neoplasia in this study is also expected to be low, because the smoking rate in Taiwanese women is as low as 4·3%.[23] Second, considering the long natural history of ICC, the 11 year follow-up period is insufficient to monitor the occurrence of ICC. We recommend a longer follow-up period study to examine how antiestrogen contributes to the risk of ICC.

In conclusion, this population-based breast cancer cohort study demonstrated that antiestrogens reduce the incidence of cervical neoplasia. In addition to supporting the estrogen dependence of cervical neoplasia in humans, this study provides a rationale for the clinical trial of antiestrogens in the treatment of cervical neoplasia.

References

1. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. *Best*

Pract Res Clin Obstet Gynaecol 2006; 20(2): 207-25.
2. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189(1): 12-9.
3. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet* 2007; 370(9590): 890-907.
4. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer* 2006; 119(5): 1108-24.
5. Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodhill A, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007; 370(9599): 1609-21.
6. Plummer M, Peto J, Franceschi S. Time since first sexual intercourse and the risk of cervical cancer. *Int J Cancer* 2012; 130(11): 2638-44.
7. Chung SH, Wiedmeyer K, Shai A, Korach KS, Lambert PF. Requirement for estrogen receptor alpha in a mouse model for human papillomavirus-associated cervical cancer. *Cancer Res* 2008; 68(23): 9928-34.
8. Chung SH, Franceschi S, Lambert PF. Estrogen and ERalpha: culprits in cervical cancer? *Trends Endocrinol Metab* 2010; 21(8): 504-11.
9. Chung SH, Lambert PF. Prevention and treatment of cervical cancer in mice using estrogen receptor antagonists. *Proc Natl Acad Sci U S A* 2009; 106(46): 19467-72.
10. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA* 2012; 308(18): 1906-14.
11. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. *Syst Rev* 2013; 2: 35.
12. Lorusso D, Petrelli F, Coinu A, Raspagliesi F, Barni S. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. *Gynecol Oncol* 2014; 133(1): 117-23.
13. Huiart L, Bardou VJ, Giorgi R. The importance of adherence to oral therapies in the field of oncology: the example of breast cancer. *Bull Cancer* 2013; 100(10): 1007-15.
14. Storer BE, Gooley TA, Jones MP. Adjusted estimates for time-to-event endpoints. *Lifetime Data Anal* 2008; 14(4): 484-95.
15. Taiwan Public Health Report 2013 pg97-99, http://www.hpa.gov.tw/English/ClassShow.aspx?No=201401170001. Accessed May 13, 2014.
16. Chao A, Hsu KH, Lai CH, Huang HJ, Hsueh S, Lin SR, et al. Cervical cancer screening program integrating Pap smear and HPV DNA testing: a population-based study. *Int J Cancer* 2008; 122(12): 2835-41.
17. Massad LS, Collins YC. Strength of correlations between colposcopic impression and biopsy histology. *Gynecol Oncol* 2003; 89(3): 424-8.
18. Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010; 28(3): 509-18.

19. Brake T, Lambert PF. Estrogen contributes to the onset, persistence, and malignant progression of cervical cancer in a human papillomavirus-transgenic mouse model. *Proc Natl Acad Sci U S A* 2005; 102(7): 2490-5.
20. Pagliusi SR, Teresa Aguado M. Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine* 2004; 23(5): 569-78.
21. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer* 2007; 120(4): 885-91.
22. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1996; 14(5): 1718-29.
23. Health Promotion Administration, Ministry of Health and Welfare, Taiwan: Bureau of Health Promotion Department of Health, Adult Smoking Behavior Surveillance System(ASBS) http://www.hpa.gov.tw/BHPNet/English/ClassShow.aspx?No=201401290001. Accessed May 13, 2014.
24. Munger K. Are selective estrogen receptor modulators (SERMs) a therapeutic option for HPV-associated cervical lesions and cancers? *Am J Pathol* 2014; 184(2): 358-61.
25. Castle PE. Do selective estrogen receptor modulators treat cervical precancer and cancer? Time to pool data from relevant trials. *Int J Cancer* 2011; 128(4): 997-8.
26. Karimi Zarchi M, Behtash N, Sekhavat L, Dehghan A. Effects of tamoxifen on the cervix and uterus in women with breast cancer: experience with Iranian patients and a literature review. *Asian Pac J Cancer Prev* 2009; 10(4): 595-8.
27. Bigler LR, Tate Thigpen J, Blessing JA, Fiorica J, Monk BJ. Evaluation of tamoxifen in persistent or recurrent nonsquamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Int J Gynecol Cancer* 2004; 14(5): 871-4.
28. Ferrandina G, Ranelletti FO, Larocca LM, Maggiano N, Fruscella E, Legge F, et al. Tamoxifen modulates the expression of Ki67, apoptosis, and microvessel density in cervical cancer. *Clin Cancer Res* 2001; 7(9): 2656-61.
29. Friedrich M, Mink D, Villena-Heinsen C, Woll-Hermann A, Schmidt W. Tamoxifen and proliferation of vaginal and cervical epithelium in postmenopausal women with breast cancer. *Eur J Obstet Gynecol Reprod Biol* 1998; 80(2): 221-5.

科技部補助計畫衍生研發成果推廣資料表

日期:2014/10/30

科技部補助計畫	計畫名稱: 雌激素與子宮頸癌等女性賀爾蒙依賴性癌症發生的關係：健康資料串聯研究與臨床前期研究
	計畫主持人: 朱堂元
	計畫編號: 102-2629-B-303-001- 學門領域: 性別主流科技計畫

無研發成果推廣資料

102 年度專題研究計畫研究成果彙整表

計畫主持人：朱堂元	計畫編號：102-2629-B-303-001-
計畫名稱：雌激素與子宮頸癌等女性賀爾蒙依賴性癌症發生的關係：健康資料串聯研究與臨床前期研究	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	1	0	100%		

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。)	於 2014 年 4 月於北京舉行的 The 6th Biennial Conference of Asia Oceania Research Organisation on Genital Infections and Neoplasia(AOGIN)，並口頭報告論文: Antiestrogens reduce the incidence of cervical neoplasia in a population-based breast cancer cohort 。

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

科技部補助專題研究計畫成果報告自評表

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、主要發現或其他有關價值等，作一綜合評估。

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：

2. 研究成果在學術期刊發表或申請專利等情形：

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 100 字為限）

無

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）

本研究以健保資料庫重大傷病檔做乳癌病人為研究世代，研究抗雌激素治療對子宮頸癌及癌前期病變之發生之影響，發現長期使用抗雌激素藥物可以明顯減少子宮頸癌及癌前病變之發生。研究結果之影響價值有下：

（一） 學術上，率先發現抗雌激素有預防子宮頸癌的效果。提出全人口群的長期追蹤的研究證據。並首度從人身上證實雌激素為子宮頸癌生成的第二元兇，證實了基因轉殖小鼠研究所發現之雌激素及雌激素受體為人類乳突病毒導致子宮頸癌化的必要關鍵。小鼠研究發現之抗雌激素藥物對子宮頸癌有治療效果，在此人群研究中也得到間接之佐證。

（二） 本研究提供以抗雌激素藥物作為子宮頸癌高危險族群（如 HPV 病毒持續感染者，子宮頸上皮低度病變者）化學預防的基礎。

（三） 本研究之結果強力支持，PI 目前執行中之 NRPB 臨床試驗計畫：「Tamoxifen 與 Letrozole 在復發或持續性子宮頸鱗狀上皮癌之療效及新生物標記：多中心、隨機分配二期臨床試驗」。