科技部補助專題研究計畫成果報告
期末報告

子宮內膜癌症之創新臨床預後指標模式與醫療科技評估

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計 畫 主 持 人 ：張啟昌

報 告 附 件 ：出席國際會議研究心得報告及發表論文

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中 華 民 國 104 年 01 月 03 日

中 文 摘 要 ： 臨床醫療決策有賴於多元實際證據的輔助分析。有鑑於過去的研究發展，文獻中臨床隨機試驗與非臨床隨機試驗設計所獲得預後指標的結論莫衷一是，對於子宮內膜癌的預後指標仍然無法獲得一致性的結論。因此，本研究計畫規劃藉由統合分析(meta analysis)的架構，藉由文獻中臨床隨機試驗與非臨床隨機試驗設計加以整合分析，以建立子宮內膜癌的預後指標模式並輔助臨床醫師施以個別化治療的策略。

本研究分別針對隨機臨床試驗使用 the modified Jadad scale；以及針對非隨機臨床隨試驗使用 the Newcastle-Ottawa Scale 方法。獲得結果之創新臨床預後指標模式為：PI=2.3xage+84 (if grade 2) or 135 (if grade 3)+69 (if stage Ib or Ic) or 127 (if stage II)+43 (if no lymphadenectomy)-57 (for adjuvant chemotherapy of 3 times or more)+24 (calibrating constant)。目前正針對本校附設醫院的癌症登記資料庫進行追溯研究分析。

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，子宮內膜癌雖尚未居於領先地位，但其數目也逐步上升，它對於子宮頸癌的比率由五十年代的 40:1(子宮內膜癌：子宮頸癌），已在近年來增高為 14:1，故子宮內膜癌病例，在臺灣的逐漸增多，可見其未來很可能會超過子宮頸癌、卵巢癌，成為本地區最常見的婦科癌症。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。

中文關鍵詞： 統合分析, 復發子宮內膜癌, 預後因子指標模式

英 文 摘 要 ： Where the available evidence comes from different sources methods are required that can synthesis all of the evidence. To further improve on outcome for patients with endometrial cancer, physicians need to identify risk factors for poor survival and develop applicable treatment strategies. Making the prognostic index allows a precise analysis by stratifying the patients, and an individual treatment according to prognosis. During last three decades, many randomized and non-randomized studies have

evaluated the prognostic factors affecting the treatment outcome of endometrial cancer. However, results of these studies were not entirely consistent； the impact of prognostic factors on endometrial cancer is still unclear.

Therefore, this project conducted a meta-analysis and synthesising evidence from studies with different designs. The methodological quality of the studies was assessed using the modified Jadad scale for randomized controlled trials (RCTs) and the Newcastle－Ottawa scale for non-RCTs. Based on the result of the prognostic index model, the equation PI=2.3×age+84 (if grade 2) or 135 (if grade 3)+69 (if stage Ib or Ic) or 127 (if stage II)+43 (if no lymphadenectomy)?57 (for adjuvant chemotherapy of 3 times or more)+24 (calibrating constant). Our PI model was predictive in this project and may be effective in clinical practice. Further prospective studies should be conducted to confirm the predictive ability of the new PI model for early-stage endometrial cancer.

In future work, 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. 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.

英文關鍵詞： Meta Analysis, Recurrent Endometrial Cancer, Prognosis Factors index Model

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）

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計畫主持人：張啟昌

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□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　103　年　12　月　31　日

1 BACKGROUND AND RATIONALE

Informed healthcare decision making depends on the available evidence base. Where the available evidence comes from different sources methods are required that can synthesis all of the evidence. The different types of study designs (e.g., randomized, non-randomized/observational) used to assess the effects of interventions can be arranged into a hierarchy, at the top of which is the randomized controlled trial (RCT) (Centre for Reviews and Dissemination, 2009). Randomization increases the likelihood that the treatment groups will be balanced in terms of known and unknown prognostic or confounding variables. Consequently the treatment effects estimated from RCTs are less subject to the potential confounding effects of extraneous variables (Gordis, 2004). Evidence from RCTs alone, however, may not be sufficient to inform decision makers. In particular, the strict inclusion and exclusion criteria which are often applied in RCTs may limit their generalizability relative to non-randomized studies (Ades et al., 2006; Prevost et al., 2000). Furthermore, the scarcity of randomized studies for certain non-drug technologies, such as medical devices and surgical procedures, may necessitate the use of evidence from non-randomized studies in addition to that available from randomized studies (Ades et al., 2006). Contrary to ignoring evidence from non-randomized studies, it has been argued that all available evidence should be used to inform healthcare decision making (Sculpher et al., 2007; Sutton et al., 2009). Such an approach requires methods capable of synthesising evidence from both randomized and nonrandomized studies.

During past fourth decade, Meta-analysis has been used to synthesize results from a wide variety of studies, both non-experimental (e.g., gender differences) and experimental (e.g., intervention effectiveness). Meta-analytic results allow for more powerful estimates of treatment effects than those estimates provided by individual studies considered in isolation (Borenstein et al., 2009). Clinical and medical decision making is based increasingly on evidence-based practices and the totality of the relevant accumulated evidence that meta-analyses provide (Sutton and Higgins, 2008). Meta-analytic results help inform practitioners of evidence-based medicine, policymakers, and regulatory bodies, about the overall efficacy of different treatment interventions. In addition, the citation impact of meta-analytic studies is profound; meta analysis are the most frequently cited type of research design in the medical literature (Patsopoulos et al., 2005). In fact, in recognition of the growing importance of meta analysis, the United States government's American Recovery and Reinvestment Act of 2009 appropriated funds for comparative effectiveness research (CER), which synthesizes research that compares treatment outcomes and efficacies. The same CER likewise considers the evidence for prevention, treatment, and diagnosis of diseases and other health conditions (H.R.1, S.1, 111th U.S. Congress, first session, 2009). A widely accepted goal of research is to produce cumulative knowledge that is generalizable, and meta analysis provide a means of addressing this goal through quantitative integration of the cumulative research on a topic. In a meta-analysis, data are converted with statistical techniques into a standardized measure of effect sizes such as standardized mean differences, odds ratios, or correlation coefficients. Converting study results into a common standard metric allows a research synthetist to make comparisons of effect sizes easily across studies (Lipsey and Wilson, 2001). A noteworthy advantage of meta-analysis is that it yields a summary effect size estimate that has considerably more power to detect effects than that of any of the individual studies. This power permits meta-analysts to uncover more meaningful effects when study results concur and to discover study-level characteristics that can help explain differences in effects among studies (Lipsey and Wilson, 2001).

In a cost-containment environment, economic evaluation plays an important role in healthcare technology assessment. The International Network of Agencies for Healthcare Technology Assessment (HTA) defines as "a multidisciplinary field of health policy analysis studying the medical, social, ethical, and economic implications of development, diffusion, and use of health technology", e.g., healthcare technologies include pharmaceuticals, devices, and surgical procedures (International Network of Agencies for Health Technology Assessment, 2013). Indeed, the economic evaluation of healthcare technologies involves the comparison of alternative interventions in terms of their relative costs and effects (Drummond et al., 2005). By comparing costs and effects, economic evaluations inform decision making regarding the efficient allocation of scarce resources. Cost-effectiveness research is used as formal inputs into decisions about which interventions and programmes should be funded from collective resources by health systems around the world (Drummond et al., 2005). The increasing use of economic evaluations to inform healthcare decision making raises important methodological issues for this area of research. One of these issues is the need to synthesis evidence on effects

from all sources of available evidence (Ades et al., 2006). Depending on the technologies being compared, the body of available evidence could include a variety of different sources (e.g., randomized controlled trials (RCTs), non-randomized/observational studies).

Bayesian statistical methods represent a valuable set of analytical tools for combining evidence from different sources (Briggs, 2001). While the application of Bayesian methods to the economic evaluation of healthcare technology is relatively new, the potential for these methods to take into account all available evidence to inform decision making is profound. A key challenge, however, is to characterize the major gaps in existing methods and to set priorities for methods research. Bayesian models combine study information, which this proposal will call current evidence, with previous information to produce new knowledge. In Bayesian terms, information from previous study is called a prior, current evidence is called a likelihood, and new knowledge is called a posterior. A posterior is produced by updating priors with current evidence, typically through random-effects meta-analysis, which accounts for variability in observed treatment effects by modeling both within and between-study variance. Bayesian random-effects models are typically used to compute the posterior distribution of the treatment effect but can be easily extended to predict the treatment effect in the future.

Depending on the types of evidence being combined, a researcher may face various methodological challenges. The specific issues addressed in this proposal are: 1) how to combine evidence from randomised and non-randomized studies, and 2) how to combine patient level data from a trial based economic evaluation with additional evidence from the literature. Therefore, this proposal will conduct a meta-analysis to summarize those studies and to develop a novel prognostic index model. Based on the result of the prognostic index model, this project also investigated when to take the critical intervention treatment, given the costs of healthcare technology assessment, is of fundamental importance. Further, Bayesian cost-effectiveness analysis is developed for a survival model based on proportional intensity Nonhomogeneous Poisson process, where individuals may expected to experience repeated events and concomitant variables are observed. The methodology is illustrated using the recurrent endometrial cancer data which medical records and pathology has reviewed for all patients accessible by our University Hospital Tumor Registry.

2. STATEMENT OF THE PROBLEM

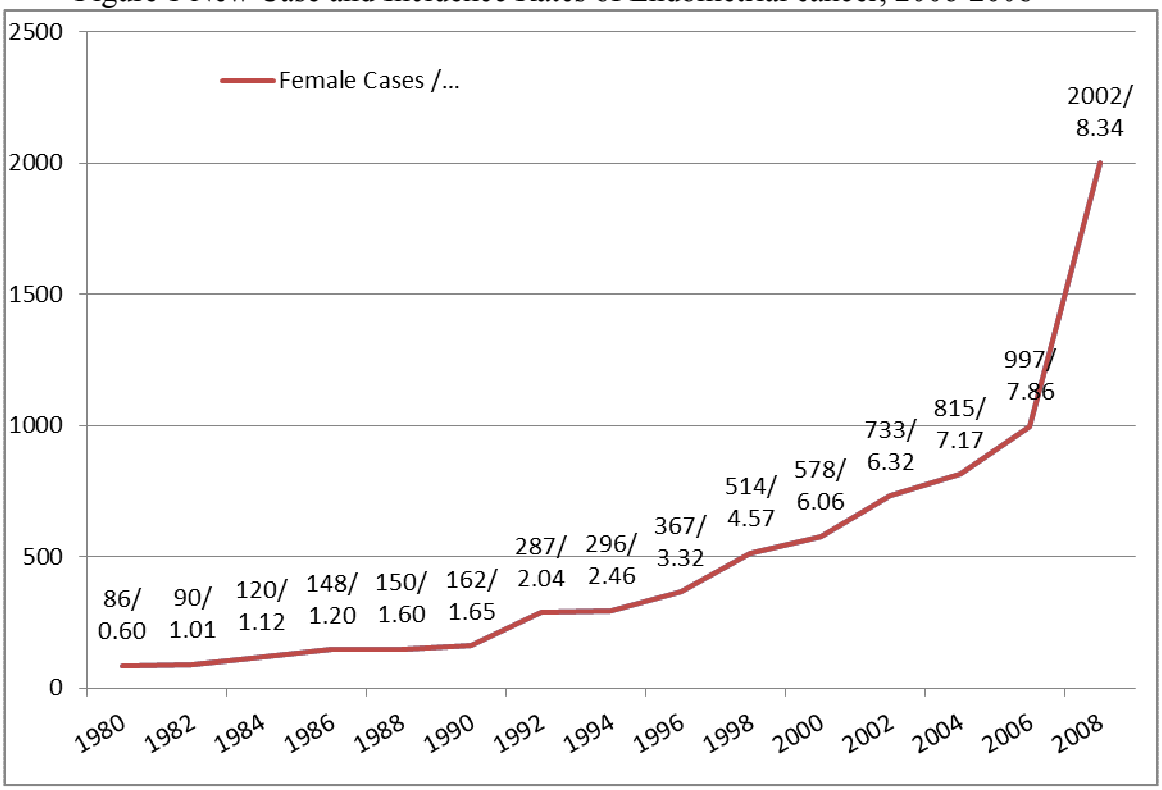
Endometrial cancer is the most common malignancy arising in the female genital tract throughout the world. It most commonly affects postmenopausal women. According to International Agency for Research on Cancer in 2005, it was diagnosed in 199,000 women worldwide and 50,000 women died of the cancer. Compared to Western and US, Endometrial cancer in Taiwan is the second common neoplasm following cervical cancer in the female genital tract. According to the data of Taiwan Cancer Registry, the annual incidence rate of endometrial cancer is greater in 2008 (8.34 per 100,000 per year) as compared to 1980 (0.6 per 100,000 per year). It is estimated that there will more than 2,400 new cases in 2013.

The cure rate of endometrial cancer is quite high if detected early, but approximately 25% of International Federation of Gynecology and Obstetrics (FIGO) stage II to stage IV disease will recur with modern multimodality treatment (American Cancer Society, 2013). 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. Probably several factors exist which indeed affect the ultimate prognosis of early stage endometrial cancer other than clinical staging. In other words, early detection of recurrence may impact survival. Moreover, detection of asymptomatic recurrences is associated with prolonged overall survival and survival from the time of initial detection of recurrence (Chang and Cheng, 2007). Therefore, this proposal attempts to improve surveillance after treatment might lead to earlier detection of relapse, and precise assessment of recurrent status could improve outcome.

The natural history of endometrial cancer has developed through evaluation of the patterns of spread. 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.

Figure 1 New Case and Incidence Rates of Endometrial cancer, 2006-2008



The main etiologic hypothesis for the development of endometrial cancer is exposure to high levels of estrogen in conjunction with inadequate progesterone. Other risk factors include obesity and nulliparity. In addition, some life-style factors may also the risk of endometrial cancer. According to the literatures, the prognostic factors affecting the treatment outcome of endometrial cancer include tumor stage, patient age, histologic type, grade, depth of invasion into the myometrium, lymph node status, lymphvascular space involvement, hormone receptors and DNA ploidy. Patients with these adverse prognostic factors should receive more aggressive treatments. Although there has been considerable progress in the treatment of malignancy over past decade, the survival rate of advanced and recurrent endometrial cancer remains poor.

To further improve on outcome for patients with endometrial cancer, physicians need to identify risk factors for poor survival and develop applicable treatment strategies. Thus, it is important to accurately predict the prognosis in endometrial cancer. Making the prognostic index allows a precise analysis by stratifying the patients, and an individual treatment according to prognosis. During last three decades, many epidemiological studies have evaluated the prognostic factors affecting the treatment outcome of endometrial cancer. However, results of these studies were not entirely consistent; the impact of prognostic factors on endometrial cancer is still unclear. Therefore, this proposal conducted a meta-analysis to summarize those studies and to develop a novel prognostic index model. Based on the result of the prognostic index model, we also investigated when to take the critical intervention treatment, given the costs of healthcare technology assessment, is of

fundamental importance.

3. AN OVERVIEW OF EVIDENCE SYNTHESIS

Beyond the importance of basing healthcare decision making on all available evidence, there may be other practical reasons to combine randomized and non-randomized types of comparative evidence. For certain healthcare technologies, especially non-drug technologies, there may be a lack of randomized studies (Ades et al., 2006). RCTs are designed to provide estimates of efficacy in an ideal setting, while non-randomized or observational studies may better reflect estimates of the effectiveness of the treatments in the real world. In exchange for the greater generalisability associated with non-randomized studies, there is also an increased likelihood of imbalances among patient characteristics due to the non-randomized nature of the studies (Grines et al., 2008). These imbalances, if not accounted for in some way, could bias the results. The extent to which bias in the results is affected by factors such as the impact of the imbalances, the relative number of randomized and non-randomized studies and the study arm sizes must also be understood.

In a meta-analysis, also known as a quantitative research synthesis, quantitative methods are used to combine statistically the results of an ensemble of similar research studies into a weighted mean and explore the consistency of the findings. Current meta-analytic methods allow a researcher to: i) estimate the magnitude of the effect size with increased power beyond that of an individual study, ii) estimate and evaluate the consistency of study outcomes across a series of studies, iii) identify study-level characteristics that are associated with differences in study outcomes, iv) delineate which treatment groups or subgroups benefit particularly from an intervention, v) estimate a prediction intervals for an effect in a new study, vi) quantify and construct a 95% confidence interval (CI) for the heterogeneity.

Fixed Effect (FE) Models

Historically, many systematic reviewers have preferred the FE model because FE models offer simpler computational formulas and are easier to conceptualize (National Research Council, 1992). With an FE model the *a priori* statistical assumption is that there is a single, underlying, true effect size μ, which is shared by all k separate studies. The assumption of the FE model is that the effect size is fixed and homogeneous across studies: $\theta_i=...=\theta_k=\mu$, where θ_i is the population effect of the ith study with an ensemble of k independent studies. FE models assume that the variance observed across studies can be attributed solely to sampling variability and that τ, the standard deviation of the between-study variation in true effect sizes, is equal to zero. In the FE model the observed effect size Y_i, for study i is represented by the population mean μ, plus the within-study sampling error: $Y_i=\mu+\varepsilon_i$ (Borenstein et al. 2009). The overall summary meta-analytic effect size is calculated by averaging effect sizes according to the weight assigned to each study. In the FE meta-analysis the weight assigned to each individual study is the inverse of the sampling variance: $w_i = \frac{1}{s_i^2}$, where s_i^2 is the within-study error variance for the ith study, which is inversely proportional to the within-study sample size (Shadish and Haddock, 2009). The overall FE treatment effect $\hat{\mu}$, is estimated as a weighted average:

$$\hat{\mu} = \frac{\sum_{i=1}^{k} w_i k_i}{\sum_{i=1}^{k} w_i} \qquad (1)$$

where the ith study reports an observed effect size of Y_i with a corresponding assigned weight of w_i (Shadish & Haddock, 2009), the numerator in the middle term equals the sum of the products of each effect size multiplied by its weight, and the denominator is the sum of the all the individual weights (Borenstein et al., 2009).The variance v_μ of the weighted mean effect size is estimated as the reciprocal of the sum of the individual study weights, $\upsilon_\mu = \frac{1}{\sum_{i=1}^{k} w_i}$, and the square root of v_μ is the estimated standard error of the mean

effect size, $SE_u = \sqrt{\sum_{i=1}^{k} w_i}$ (Borenstein et al., 2009). It is important to note that the FE formula for the weights assigned to each study and the standard error of estimate of the average effect size *does not* include a term for the variance observed between studies, because this term is assumed to be zero.

Therefore, synthesizing the results of studies that vary in design, populations sampled, and treatment protocols will inevitably result in a compilation of effect sizes that has an inherent element of diversity (Higgins and Thompson, 2002), and it can be argued that there is always going to be some variation across studies (National Research Council, 1992), making FE estimates invalid. Higgins et al. (2009) note that the FE assumption of homogeneity of effect sizes is often untenable for studies in biomedicine because these studies are likely to differ from each other on numerous dimensions such as populations, settings, treatments, outcomes and they recommend avoiding the use of FE models. Many researchers have recognized the limitations with FE meta-analytic methods and have advocated the use of other methodological options such as random effect models (Schmidt et al., 2009; Kisamore and Brannick, 2008).

Random Effect (RE) Models

Formal exploration of the between-study variation with random effects modeling has increasingly been recognized as a necessary and worthwhile meta-analytic endeavor, because explanation of the variation will often result in a better and more thorough understanding of the treatment effect under investigation. Random effects model explicitly account for the heterogeneity with a parameter that represents the between-study variation. Sutton and Abrams (2001) express the assumptions of the RE meta-analytic models as $Y_i \sim N(\theta, \sigma^2)$, where Y_i is assumed to come from a normal distribution with a known sampling variance, and $\theta_i \sim N(u,\tau^2)$, where the true underlying effect sizes, θ_i, are assumed to come from a normal distribution of effect sizes with mean u and variance τ^2, which represents the between-study variation of each θ_i around μ. However, in practice, this normal distribution assumption for the underlying effects in individual studies is a strong assumption, which is often made without supporting evidence in favor of the assumption (Higgins, et al., 2009). The simple (no covariates) RE model is expressed as

$$Y_i = \mu + \delta_i + \varepsilon_i \tag{2}$$

where μ is the overall mean, δ_i, is the deviation of study i's true effect from the grand mean, and ε_i is the error deviation of study i's observed effect size from the true effect size (Borenstein et al., 2009).

The different assumptions of the FE and RE models (i.e., FE assumes $\tau = 0$ and RE allows $\tau > 0$) result in differing formulas for the standard error of the mean effect size, an important statistic that is used both in confidence interval computation and for significance testing of the mean (Schmidt et al., 2009). Raudenbush (2009) recognizes RE models as advantageous because these modeling procedures help i) quantify heterogeneity in true effect sizes, ii) include the between-study variation in confidence interval estimates, iii) extend easily to investigate the ability of study-level variables (covariate) to account for variation, iv) derive improved estimates of effect sizes in individual studies, and v) conceptualize the random effect in a manner that is consistent with the scientific goal of generalization. In order to compute the overall RE weighted mean effect, the weighting scheme w_i^*, that is assigned to each study is inversely proportional to its within study and between-study variance (Borenstein et al., 2009).

$$w_i^* = \frac{1}{\sigma_i^2 + \tau^2} \tag{3}$$

These weights are then used to compute the overall summary mean effect μ, where

$$\mu = \frac{\sum_{i=1}^{k} w_i^* y_i}{\sum_{i=1}^{k} w_i^*} \quad (4)$$

Here μ is equal to the sum of the products of the RE weights multiplied by each effect size divided by the sum of the weights (Borenstein, et al., 2009). The summary effect μ, has a variance V_μ^*, that is estimated as

$$V_\mu^* = \frac{1}{\sum_{i=1}^{k} w_i^*} \quad (5)$$

and the standard error of μ, $SE_{\mu*}$, is estimated as $SE_{\mu*} = \sqrt{V_\mu^*}$ (Borenstein et al., 2009). A RE 95% confidence interval about μ is expressed as $\mu \pm 1.96(SE_{\mu*})$ based on the normal distribution.

Mixed Effect Model

Raudenbush and Bryk (2002) represent the RE meta-analytic model as a two-level hierarchical linear model, because meta-analytic data has an inherent hierarchical structure where the subjects are nested within studies. Raudenbush and Bryk (2002) describe the model as a two-stage sampling design where the sampling mechanism results in two components of variance (e.g., random effect variance at the study level and estimation variance at the subject level). The random effect variance is the variance that arises as a result of sampling a random sample from a larger universe of studies that vary in their true effect sizes. The estimation variance occurs because each study's effect size estimate is based on a limited number of subjects (Raudenbush, 2009).

Level-1 model

Raudenbush(2009) expresses the Level-1 (Within Studies) model as $Y_i = \theta_i + e_i$, where Y_i is the observed effect size estimate for study *i,* θ_i represents the true effect size for each of the $i=1,..., k$ studies, and e_i is the sampling error. The sampling errors e_i are assumed to be statistically independent from each other, and they come from a normal distribution with a mean of zero and a known variance σ_i^2, where σ_i^2 reflects the within-study sampling variance and the sample size of study: $e_i \sim (0, \sigma_i^2)$.

Level-2 model

The Level-2 model includes study-level covariates (also termed effect modifiers, explanatory variables, and treatment interactions) that can be added to the meta-analytic model to help explain some of the heterogeneity, so that the estimate of τ^2 represents the remaining variation in θ_i that is not explained by the study covariates. In the Level-2 model, the true unknown effect size depends on both fixed study characteristics and the level-2 random effect (Raudenbush and Bryk, 2002). The Level-2 (Between-Studies) prediction model is expressed by Raudenbush (2009) as more general than other models: $\theta_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_p x_{ip} + \delta_i$, where β_0 represents the model intercept; $x_{i1},..., x_{ip}$ represents the coding of the study-level characteristics; $\beta_1,...\beta_p$ are the regression coefficients, which can be used to predict differences in the individual study effect sizes θ_i; and δ_i is the random effect of the i^{th} study. The random effect, $\delta_i \sim (0, \sigma_i^2)$ is usually assumed to come from a normal distribution with mean zero and variance τ^2 (Raudenbush, 2009).

These two models can be combined into a mixed-effects linear model (also referred to as a hierarchical linear model or a generalized linear mixed model): $Y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_p x_{ip} + \delta_i + e_i$, with the assumption that $\delta_i + e_i \sim N(0, v_i^*)$, where $v_i^* = \tau^2 + \sigma_i^2$ represents the total variance of the observed effect size (Raudenbush, 2009). Two types of point estimation methods that are commonly used to estimate τ^2 in random/mixed-effect meta-analytic models include DerSimonian and Laird (1986) and Restricted Maximum Likelihood Estimation (REML).

In a random/mixed-effects approach the random-effect variance is treated as if it were known even though it is

estimated, and thus when τ is estimated from the data, the uncertainty of the estimate is not considered. The overall mean meta-analytic effect size estimate and regression coefficients are weighted estimates that are dependent upon the uncertainty in the variance of the random effects (Raudenbush, 2009). Not considering the underlying uncertainty in the estimate of the RE variance may result in threats to the validity of statistical inference from the meta-analysis (Raudenbush, 2009). Meta-analytic estimates are often based on a limited number of data points and this further compromises the validity of the between-study variance estimate and the confidence intervals about μ. When the number of included studies k is small, when the sample size within studies n is small, or when the sampling variance v_i, is large, methods that estimate τ as a fixed value underestimate the standard errors and the corresponding confidence limits, which may result in inaccurate overall estimates of μ (DuMouchel, 1994; Raudenbush, 2009). Furthermore, in practice it is often not plausible to assume that the random effects are normally distributed with constant variance (Hardy and Thompson, 1998).

Bayesian Hierarchical Linear Model

Bayesian methods offer the advantage of encouraging the use of a unified and model-based approach to evidence synthesis (Sutton and Higgins, 2008; DuMouchel and Normand, 2000). The Bayesian statistical philosophy is essentially about updating probabilities in light of new evidence and thus it translates well into the practice of quantitative research synthesis and updating of meta-analyses. The Bayesian approach distinguishes itself from traditional meta-analytic methods because Bayesian analyses emphasize estimation and prediction of parameters and uncertainty assessments (National Research Council, 1992). When the uncertainty of τ is not considered in a meta-analytic model, as is the case in the random/mixed-effects models, it is possible that a treatment effect may be incorrectly identified as significant (DuMouchel and Normand, 2000). Comparative studies have shown that the problem with the RE approach is that, because the uncertainty in the RE variance estimate is not considered, τ may not be estimated accurately when there are a small number of studies (Spiegelhalter et al. 2004).

The essential concept in the Bayesian approach to research synthesis is the notion of exchangeability of study effects (Higgins, et al. 2009). Within a Bayesian framework, study effects are considered to be similar to each other but not identical (Spiegelhalter et al., 2004; Higgins et al., 2009). Although the Bayesian model is similar to an RE model, it differs conceptually from the RE model in the exchangeability assumption and the justification for the process that generates the random effects (Raudenbush, 2009). According to the Bayesian perspective, the random variation of the true effect sizes reflects the investigator's lack of knowledge (uncertainty) about the process that generates the random effects, while a traditional RE model specifies the sampling mechanism of the sampling studies from a larger population of studies as the source of random effects variance (Raudenbush, 2009). In Bayesian statistics every unknown model parameter has its own probability distribution. This allows for direct probability statements (i.e., computation of the probability that an effect is greater than zero) and uncertainty estimates to be made about the data. Bayesian models may incorporate other relevant information about parameters that is external to the actual meta-analytic data but available to the researcher (Schmidt, 2001). The researcher's probability beliefs about the external evidence can be modeled with a 'prior' quantitative summary of the variance that reflects the researcher's uncertainty about the mean of the true effect size. This prior evidence is then formally combined with the observed meta-analytic data (known as the likelihood) via the application of Bayes' theorem and merged into the *current state of knowledge* (Sutton et al., 2000) regarding the meta-analytic outcome or intervention. Bayesian methods address the question of how beliefs about an outcome change in light of the evidence generated by the new study or meta-analysis (Sutton et al., 2000), which makes Bayesian methods particularly suitable for updating meta-analytic data.

With a Bayesian approach, the research synthetist can effectively consider and include small studies and extreme results (Smith et al., 1995), while at the same time allowing for moderate violation of the statistical assumption that effect size estimates have normal distributions with known variances (DuMouchel,1994), which can be a restrictive assumption with some types of data. Bayesian models provide more accurate estimates of study-specific parameters, θ_i, by incorporating the information from all of the studies in a meta-analysis (i.e., by borrowing strength from the other studies) in order to provide a better estimate of each individual study's effect size. The parameters that require estimation are: μ, τ, θ_i, and β (DuMouchel, 1994).

DuMouchel (1994) uses the following equations for a Bayesian meta-analysis:

$$Y_i = \mu + \delta_i + \varepsilon_i \quad (6)$$

where the observed effect size estimate derived from the ith study is denoted by Y_i. The effect size estimates from each study are assumed to be normally distributed with a known variance σ_i^2, which is conditional on the true parameter value $y_i | \theta_i \sim \mathrm{N}(\theta_i, s_i^2)$. The study-specific parameters, which are the expectation of Y_i are represented by θ_i, where $\theta_i = \mu + \delta_i$. The random effect , is assumed to be normally distributed with a mean of 0 and variance τ^2. The sampling error associated with Y_i is represented by ε_i. It is assumed to be normally distributed with a mean 0 and a *known* sampling variance: $\varepsilon_i \sim (0, s_i^2)$. Both random effects δ_i, and the within-study sampling errors ε_i, are assumed to be independent of each other and independent across studies. Equation 6 can be easily be generalized and expanded to include study-level covariates (moderator variables) which represent fixed characteristics of the studies and are used to explain variation between studies:

$$Y_i = (X_i \beta + \delta_i) + \varepsilon_i \quad (7)$$

$$\theta_i = X_i \beta + \delta_i \quad (8)$$

DuMouchel (1994) uses the term $X_i\beta$ to replace μ; where $X_i\beta$ represents a linear combination:

$$X_i\beta = \beta_0 + \beta_1 x_{i1} + \ldots\ldots + \beta_J x_{iJ} \quad (9)$$

There are three sources of variation to be estimated in a hierarchical Bayesian meta-analysis: i) s_i, the within-study random sampling error which is usually assumed to be known, ii) β, the between-study differences that can be explained by fixed study-level characteristics at the second level of the hierarchical model, and iii) τ, the standard deviation of the unexplained random variation due to differences between studies (DuMouchel, 1994; DuMouchel and Normand, 2000). In Bayesian hierarchical models it is τ, the standard deviation of the random effects variance, that plays a crucial role in assessing the uncertainty about μ and in predicting future θs (DuMouchel, 1994; Spiegelhalter et al., 2004). In a Bayesian model prior distributions are assigned for μ, τ, and β. The Bayesian hierarchical linear model can be expressed in notation as (Sutton and Abrams, 2001):

$$Y_i \sim N(\theta_i, s_i^2)\ i=1,\ldots, \quad (10)$$

$$\theta_i \sim (\mu, \tau^2) \quad (11)$$

It is through the specification of a prior distribution for τ that the Bayesian framework provides a technique for investigating the similarity of studies and the extent to which studies can borrow information from the entire ensemble of studies (Greenhouse and Iyengar, 2009). The choice of the prior distributions affects both the width of the credible interval estimates for μ and the amount of shrinkage imposed on the θ_{i*} (Pauler and Wakefield, 2000) as well as the size and width of the credible intervals for θ_{new}. However, there is no single, generally accepted, correct prior distribution that is used as a default or reference prior in Bayesian meta-analysis (Spiegelhalter et al., 2004). For this reason a Bayesian analysis often includes specification from a community of prior distributions. Prior distributions can be specified in such a way that so that FE and RE models become special cases of the Bayesian Hierarchical Linear Model (DuMouchel and Normand, 2000). For example, the meta-analytic model can reduce to the equivalent of an FE model when the prior for τ is set near the value of $\tau=0$, so that there is assumed to be one underlying common effect. Alternatively, when the number of studies in the meta-analysis is very large or when the prior for τ is concentrated around the estimate of τ, then the meta-analytic model becomes equivalent to a RE model.

Posterior probability distributions are estimated via the application of Bayes' Theorem for the parameters (i.e., τ^2, μ and β) given the data from studies Y_i...Y_k. The posterior probability distribution represents the conditional distribution of the unknown quantity of interest, given the data. The posterior distribution is

obtained by multiplying the prior probability density function by the likelihood function that represents information about the unknown quantity provided by the current data. The posterior density function is used in a Bayesian analysis for all inferences made regarding the unknown quantities of interest (Sutton et al., 2000). It is important to note that Bayesian meta-analytic results are especially dependent upon the posterior distribution of the random effect (DuMouchel, 1994). Posterior distributions for the model parameters are best understood and displayed with trace plots that graph the posterior expectation of μ and θ_i, given the posterior distribution of τ (DuMouchel, 1994). The posterior distribution of τ is often skewed and because of the skewness, the median of the distribution is commonly used for point estimation instead of the mean (Higgins et al., 2009). Computation of the posterior probability distributions requires integral calculus (i.e., calculation of the area under the curve of *f(x)*). Such integration can be exceptionally difficult and complex particularly when additional unknown parameters, termed nuisance parameters, are present (Spiegelhalter et al., 2004), thus requiring the integrals to be evaluated over several dimensions. In such situations, posterior distributions are best calculated with computer-based simulation methods such as Monte Carlo methods that evaluate these complex integrations via simulation rather than algebraic analysis (Spiegelhalter et al., 2004). Gibbs sampling is a type of MCMC method that successively samples variables from the posterior conditional distributions of each parameter (Sutton and Abrams, 2001). With this method the unknown quantities are given initial values and successive samples are obtained from the conditional distribution of each variable, given the current sampled value of the other variables, with the premise that sampling will eventually occur from the correct posterior distribution of the unknown parameters (Smith et al., 1995).

In Bayesian analysis, intervals containing 95% probability are termed *credible* or *posterior* intervals. Bayesian 95% credibility intervals can be distinguished from the traditional 95% Neyman-Pearson confidence interval in several important ways (Spiegelhalter et al., 2004). The Bayesian 95% probability interval is interpreted as the 95% probability that the true underlying θ lies in the 95% Bayesian credible or posterior interval, whereas the traditional 95% confidence interval is theorized to represent a long repeated series of confidence intervals in which 95% of these intervals should contain the true underlying parameter value (Spiegelhalter et al., 2004). Furthermore, Bayesian credibility intervals can be narrower than traditional confidence intervals as a result of the addition of prior information into the conceptual framework of the meta-analytic model (Spiegelhalter et al., 2004). The Bayesian framework offers the advantage of determining the probability that a parameter is less or greater than a specific value with the use of posterior distributions for the parameters. In a Bayesian analysis, the probabilities are estimated as the proportion of MCMC iterations in which the parameter is greater than a pre-specified value (Higgins et al., 2009). Higgins et al. (2009) support the computation of posterior probabilities as a good alternative to classical meta-analysis hypothesis testing.

Therefore, Bayesian research synthesis methods offer many desirable modeling properties over more traditional meta-analytic methods particularly in the typical case of a meta-analysis of a small number of studies. Schmid (2001) supports the use of Bayesian models because Bayesian models provide a statistically informative summary of the parameters, incorporate all sources of variation into one model, and do not require normal distributions. Furthermore, Sutton and Abrams (2001), and Sutton et al. (2000) recognize the following advantages of Bayesian methods, because these methods offer: i) full modeling of parameter uncertainty, ii) inclusion of the totality of evidence by allowing the consideration of other pertinent evidence (i.e. non-randomized evidence or expert opinion) that may otherwise be excluded by traditional methods, and iii) flexibility and extendibility with more complex data.

Recently, Bayesian hierarchical modeling has been proposed for synthesizing evidence from randomized and non-randomized studies. Prevost et al. (2000) applied their method to combine evidence relating to the relative risk for mortality from five randomized trials and five non-randomized studies evaluating mammographic screening. Other applications of Prevost's model include Grines et al. (2008) and Sampath et al. (2007). As an extension to the model, Prevost et al. (2000) proposed the inclusion of study covariates to explain differences in mean effects at the study type level. Although this is important, the authors did not model differences between study arms, which may be a limitation of this approach when dealing with non-randomized studies due to potential differences in baseline characteristics. Adjustment made using aggregate values will not account for potential imbalances between study arms resulting from the lack of randomization. Another extension proposed by Prevost made use of a prior constraint, reflecting the

assumption that evidence from non-randomized studies, having been derived from study designs with potential weaknesses (Ades et al., 2006), may be more biased than evidence from randomized studies. The effect of the prior constraint is to down weight the evidence from the non-randomized studies. This approach has been criticized as it may not eliminate bias (Eddy et al., 1990). Therefore, the objective of this proposal was to extend the Bayesian three-level hierarchical model developed by Prevost et al. (2000) in order to accommodate the greater potential for bias among the non-randomized studies by adjusting study estimates for potential confounders using differences in patient characteristics between study arms. Modeling differences between study arms is important in order to correct for potential imbalances within studies which could bias the results.

4. MATERIALS AND METHODS

Informed healthcare decision making depends on the available evidence base. Where the available evidence comes from different sources methods are required that can synthesis all of the evidence. The objective of the first year is to adopt meta-analysis method as combining evidence on effects from randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs). The research method for establishing a prognostic index model involves collecting a sufficient size of samples and developing the reliability of hazard ratio for survival for each prognosis factor.

- ***Setting***

  In general, overall survival is the optimal endpoint of clinical study; however, this requires a substantial timeframe and a vast sample size. For endometrial cancer, recurrence-free survival is a more suitable endpoint in prognosis.

- ***Search Strategy***

  A systematic literature search up to December 2013 will be performed in MEDLINE (from January 1998), SCOPUS (from May 1994) and Cochrane Library (from January 1985). Search terms using the keywords: “endometrial cancer”, “prognosis”, “prognostic factor” and “recurrence”. The titles and abstracts will be scanned to exclude any clearly irrelevant studies. The full texts of the remaining articles will be read to determine whether they contained information on the topic of interest. Furthermore, to find any additional published studies, a manual search will be performed by checking all the references of retrieved articles. All searches will be conducted independently by two clinical physicians. At last the results be compared, and any questions or discrepancies be resolved through iteration and consensus.

- ***Evaluating the quality of the literature***

  The methodological quality of the studies will be assessed using the modified Jadad scale for RCTs and the Newcastle-Ottawa scale for non-RCTs.

- ***Data Analysis***

  The three-level Bayesian hierarchical model proposed by Prevost et al. (2000) extends the standard two-level random-effects meta-analysis (Spiegelhalter et al., 2004) to include an extra level to allow for variability in effect sizes between different types of evidence (e.g., randomized versus non-randomized study designs). In addition to variability between study estimates within each study type, this model has the capacity to deal with any added uncertainty due to study design (Ades and Sutton, 2006). The three levels allow for inferences to be made at the study, study type, and population levels. Although the model can accommodate more than two types of study designs, the application presented by Prevost et al. (2010) combined evidence from two study types, randomized and non-randomized. This model can be written as follows:

$$y_{ij} \sim \text{Normal}(\psi_{ij}, s_{ij}^2) \tag{12}$$

$$\psi_{ij} \sim \text{Normal}(\theta_i, \sigma_i^2) \tag{13}$$

$$\theta_i \sim \text{Normal}(\mu, \tau^2) \quad (14)$$

where $i = 1$ or 2 for the 2 study types; $j = 1,...,k_i$ studies

At the first level of the model (12), y_{ij} is the estimated log relative risk in the jth study of type i, which is normally distributed with mean ψ_{ij} and variance s_{ij}^2. The ψ_{ij} represent the underlying effect, on the log relative risk scale, in the jth study of type i. At the second level of the model (13), the ψ_{ij} is distributed about an overall effect for the ith type of study θ_i, with σ_i^2 representing the between-study variability for studies of type i. At the third level of the model (14) the study-type effects are distributed about an overall population effect, μ, with τ^2 representing the between-study-type variability. To try to explain between study heterogeneity, Prevost et al. (2010) extended their model to include a covariate for age at the study type level. This is shown in the equation below.

$$\psi_{ij} \sim \text{Normal}(\theta_i + (\alpha \times x_{ij}), \ \sigma_i^2) \quad (15)$$

In equation 15, x_{ij} take the values of 0 and 1 for studies of patients aged less than 65 years and studies of women 65 years and over, respectively. The same approach was used by Sampath et al. (2007) to adjust for study covariates representing continuous variables such as average age and proportion of males in each study. Grines et al. (2008) did not conduct covariate adjustment but rather used funnel plots to assess heterogeneity among individual study estimates.

While heterogeneity refers to unexplained variation, bias refers to systematic deviations from the true underlying effect due, for example, to imbalances between studies arms (Centre for Reviews and Dissemination, 2004). One potential source of bias is confounding (Greenland, 2005), where an extraneous factor is associated with both the exposure under study (e.g., treatment) and the outcome of interest, but is not affected by the exposure or outcome (Rothman et al., 2008). Only when the groups being compared are balanced in all factors, both those that can be measured and those that cannot, that are associated with exposure and that affect the outcome (other than treatment) will it be certain that any observed differences between the groups are due to treatment and not the result of the confounding effects of extraneous variables. Randomization increases the likelihood that the groups will be balanced not only in terms of the variables that we recognize and can measure but also in terms of variables that we may not recognize and may not be able to measure (i.e., unknowns) but that nevertheless may affect the outcome (Gordi, 2004). In contrast, the greater likelihood of imbalances within the non-randomized studies could have implications especially when combining both types of study designs. In order to deal with this problem, we will extended Prevost's three-level model to adjust for differences within studies rather than adjusting for aggregate values at the study type level as in equation 15. The proposed approach uses the variation in imbalances across studies to adjust for differences in patient characteristics between treatment arms within studies. As with RCTs, the resulting balance in patient characteristics within studies should avoid the influence of confounding.

The following presents an extension of Prevost's model based on odds ratios, but could be extended to relative risk. This analysis will be undertaken using a binomial model in which the odds of the event are calculated for each study and study arm level information is incorporated in the model. The proposed model can be written as follows:

$$r_{C_{ij}} \sim \text{Binomial}(P_{C_{ij}}, n_{C_{ij}}) \quad \text{and} \quad r_{T_{ij}} \sim \text{Binomial}(P_{T_{ij}}, n_{T_{ij}}) \quad (16)$$

$$\text{log odds}(P_{C_{ij}}) = \gamma_{ij} \ \text{and} \ \text{log odds}(P_{T_{ij}}) = \gamma_{ij} + \psi_{ij} \quad (17)$$

$$\psi_{ij} \sim \text{Normal}(\theta_i + \sum_{m=1}^{M} \alpha_m (x_{mTij} - x_{mCij}), \ \sigma_i^2) \quad (18)$$

$$\theta_i \sim \text{Normal}(\mu, \tau^2) \quad (19)$$

where i = 1 or 2 for the 2 study types j = 1,...,k_i studies, m = 1,..,M confounders. It is assumed that the number of events in each arm in the jth study of type i follows a binomial distribution defined by the proportion of patients who experience the event in each arm in the jth study of type i and the total number of patients in each arm in the jth study of type i, as shown in Equation 17 describes the log odds for the event in the control γ_{ij} and treatment $\gamma_{ij} + \psi_i$ arms of each of the k_i studies.

This proposed model assumes that the log odds ratio ψ_{ij}, follows a normal distribution with a mean which is the sum of θ_i (i.e., the overall intervention effect in the ith type of studies) and a study specific bias adjustment, $\alpha_m(x_{mTij} - x_{mCij})$, that is proportional to the relative differences between the study arms in each of the studies. In this expression, x_{mTij} and x_{mCij} are the values of the mth potential confounder in each of the study arms in the jth study of type i while α_m represents the mean bias for the mth potential confounding variable, across all the studies. All of the analyses will be conducted using MCMC simulation implemented. The generated parameter values were monitored and summary statistics such as the median and 95% credible interval of the complete samples will be obtained. In addition, data will be analyzed using the Comprehensive Meta-Analysis software. The results will be expressed as pooled hazard ratios and 95% confidence intervals. Study-to-study variation be assessed using the Higgins I^2 test. When significant heterogeneity (p-value ≤ 0.1 or $I^2 \geq 50\%$) is not observed between the subgroups, the fixed effects model will be used, or the random effects model will be used.

- ***Prognostic Index Model***

When a pooled hazard ratio for each prognosis factor has found through meta-analysis, the regression coefficient, drawn by applying a regression function to the pooled hazard ratio will be expressed as the weight value for each prognosis factor. The prognostic index can be expressed in $PI\ Formula = \alpha_1 x_1 + \alpha_2 x_2 + ... + \alpha_n x_n$ where x is the prognosis factor significantly affecting recurrence-free survival on meta-analysis, and α is the regression coefficient for the pooled hazard ratio.

- ***Application of the PI model - Clinical Risk estimation***

Applying this PI Model to 179 patients diagnosed with endometrial cancer at our university hospital, the patients will be divided into three groups depend on their PI values. The plan is to execute recurrence-free survival analysis through Kaplan-Meier methods and thus to evaluate the significance in recurrence prediction of endometrial cancer. In addition, the PI value to maximize sensitivity and specificity will be found with respect to the occurrence of recurrence in these patients. Further, patients will be divided into two groups (high/low-risk) and Cox regression test will be executed, which is the method to obtain the cutoff PI value to maximize the hazard ratio for recurrence prediction. Finally, the SPSS software will be used for survival analysis, and p-values ≤ 0.05 will be considered statistically significant.

5. THE RESULT OF THIS PROJECT

In this study, we ultimately enrolled 8 studies (Zullo et al., 2012; Wei et al., 2009; Humber et al., 2007; Palomba et al., 2009; Liu et al., 2014; Esposito et al., 2014; Shim et al., 2014; Huang et al., 2013). Among them, some of the studies were RCTs (Zullo et al., 2012; Wei et al., 2009; Humber et al., 2007; Palomba et al., 2009) and some were observational studies (Liu et al., 2014; Esposito et al., 2014; Shim et al., 2014; Huang et al., 2013). The results of intervention effects for hazard ratios, as proposed in these studies, were as follows. The methodological qualities and the results of the studies included in this meta-analysis are summarized in Table 1.

For tumor grade of cell carcinoma, based on the references (Zullo et al., 2012; Ran et al., 2014) that it reflects a bad prognosis beyond poor differentiation, it was included in grade 3. As the result of a fixed effects model (I2=0.03%), tumor grade 2 demonstrated a significant hazard ratio (HR) compared to grade 1 in terms of RFS (HR=2.11, 95% CI; 1.86-3.57). As for tumor grade 3, a random effects model was applied (I2=75.3%), demonstrating a significant HR of about 2.37 times that of grade 1 (HR=2.38, 95% CI; 1.55-4.07). The literature review of FIGO substage was as follows. The result of multivariate analysis comparing stage Ia and stage Ib was only suggested in the study of Barry et al. (2014), and stage Ib was found to show a significant

HR in RFS of 1.59 times that of stage Ia (HR=1.58, 95% CI; 1.47-2.66). Considering the reports by Barry et al. (2014) and Zullo et al. (2012), there was no significant difference between stage Ic and stages Ib, and thus stage Ic and stage Ib were assumed to show the same HR. As for stage II, the fixed effects model was applied (I2=0.02%), and as a result, it showed a significantly higher HR of 2.22 times that of stage I (HR=2.14, 95% CI; 1.87-2.63). However, stage I here included all stages of Ia, Ib, Ic, so correction of the above HR was inevitable. This study assumed the situation with maximized risk to determine the HR. Therefore, the final HR of stage II took stage Ia as reference, and was processed as the multiple of stage Ib and the aforementioned pooled HR. The final HR of stage II was determined to be 3.51(reference: stage Ia).

Table 1 The methodological qualities and the results of the selected studies

Researcher(s)	Type	The quality of methodologies
Zullo et al. (2012)	RCT	modified Jadad Score: 7 (high)
Wei et al. (2009)	RCT	modified Jadad Score: 5 (high)
Humber et al. (2007)	RCT	modified Jadad Score: 5 (high)
Palomba et al. (2009)	RCT	modified Jadad Score: 6 (high)
Liu et al. (2014)	Non- RCT/ Observational studies	Newcastle-Ottawa Score: 5 stars (high)
Esposito et al. (2014)	Non- RCT/ Observational studies	Newcastle-Ottawa Score: 5 stars (high)
Shim et al. (2014)	Non- RCT/ Observational studies	Newcastle-Ottawa Score: 6 stars (high)
Huang et al. (2013)	Non- RCT/ Observational studies	Newcastle-Ottawa Score: 5 stars (high)

According to the study of Wei et al. (2009), those over 55 years of age upon multivariate analysis have been reported to show a significant HR compared to those below 55 years (HR=1.67, 95% CI; 1.51 – 2.37). Also in the large-scale multi-institutional retrospective study (Palomba et al., 2009), 1 year increase in age led to a significant increase (1.17 times) in HR (HR=1.35, 95% CI; 1.07-1.18). In this study, while other prognosis factors were categorical variables, age was the only consecutive variable. Inadequate staging where lymphadenectomy was not executed had a significantly higher risk for recurrence of about 1.87 times that of an optimal staging procedure including lymphadenectomy (HR=1.77, 95% CI; 1.53 – 2.64). Also, cases with postoperative adjuvant chemotherapy of 3 cycles or more showed significant HR of 0.74 times that of cases with observation (HR=0.81, 95% CI; 0.67-0.98). In cases of histologic cell type, it is the predominant conclusion that the results of related references (Liu et al., 2014) shows insignificant HR, and thus this paper concluded that the influence of histologic cell type recurrence on early-stage was not significant. After finding the regression coefficient for each of the pooled HR above, the PI formula was proposed as follows. PI=2.3× age+84 (if grade 2) or 135 (if grade 3)+69 (if stage Ib or Ic) or 127 (if stage II)+43 (if no lymphadenectomy)− 57 (for adjuvant chemotherapy of 3 times or more)+24 (calibrating constant).

6. DISCUSSION AND CONCLUSION

In our study, there are five factors (age, tumor grade, FIGO stage, optimal staging including lymphadenectomy, and postoperative adjuvant chemotherapy) selected as independent prognosis factors. It is the dominant opinion so far that CA125 does not reflect the prognosis for recurrence in early-stage. Also, Histologic cell type was not included in the PI formula as well. As all the resources used in our study targeted Western people, the issue of ethnic factors of whether these research results can be applied to Taiwanese needs to be addressed. The limitation of this study is that our meta-analysis included non-RCTs and RCTs which were different in study design. The risk of bias in non-RCTs is higher than in RCTs. Especially, in cases where the variables of non-RCTs included in meta-analysis vary, it would be unreasonable to integrate the result values. However, it does not imply that meta-analysis cannot be executed at all, and eventually the meaning of the result values integrated by the meta-analysis becomes limited.

As all result values of RCTs and non-RCTs used in our study were obtained by multivariate Cox regression analysis only, they might be sufficiently compensated for by the influence of other variables. In addition, most

result values of non-RCTs had homogeneity similar to those of other RCTs in our study. Therefore, it would be possible to acknowledge the legitimacy of our meta-analysis integrating the results of RCTs and non-RCTs. In conclusion, the PI formulas proposed in this study were able to distinguish high-risk and low-risk groups for recurrence of early stage allowing it to be an important resource for the selection of appropriate treatment options for patients according to recurrence risk. In the future, through a large-scale multi-institutional study, the utility and applicability of the PI formula hypothetically proposed in this report should be further studied.

To our knowledge, this is the first study to investigate the prognostic index model for endometrial cancer in Taiwan. The greatest strength of this study was the used of meta-analysis to help extract clinical information from the existing literature. In future work, 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. 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.

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【計畫成果自評】

目標達成度：100%

計畫成果：臨床醫療決策有賴於多元實際證據的輔助分析。有鑑於過去的研究發展，文獻中臨床隨機試驗與非臨床隨機試驗設計所獲得預後指標的結論莫衷一是，對於子宮內膜癌的預後指標仍然無法獲得一致性的結論。因此，本研究計畫藉由統合分析(meta analysis)的架構，並進一步延伸貝氏階層模式方法(Bayesian hierarchical model)，藉由文獻中臨床隨機試驗與非臨床隨機試驗設計加以整合分析，建立子宮內膜癌的預後指標模式並輔助臨床醫師施以個別化治療的策略。

臨床後續發展：本研究分別針對隨機臨床試驗使用 the modified Jadad scale；以及針對非隨機臨床隨試驗使用 the Newcastle–Ottawa Scale 方法。獲得結果之創新臨床預後指標模式為：PI=2.3×age+84 (if grade 2) or 135 (if grade 3)+69 (if stage Ib or Ic) or 127 (if stage II)+43 (if no lymphadenectomy)−57 (for adjuvant chemotherapy of 3 times or more)+24 (calibrating constant)。目前正針對本校附設醫院的癌症登記資料庫進行追溯研究分析。

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，子宮內膜癌雖尚未居於領先地位，但其數目也逐步上升，對於子宮頸癌的比率由五十年代的 40:1(子宮內膜癌：子宮頸癌），已在近年來增高為 14:1，故子宮內膜癌病例，在臺灣個案逐漸增多，可見其未來很可能會超過子宮頸癌、卵巢癌，成為本地區最常見的婦科癌症。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

日期：___年___月___日

計畫編號	MOST　　102-2633-E-040 -001　—		
計畫名稱	子宮內膜癌症之創新臨床預後指標模式與醫療科技評估		
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	102 年 10 月 19 日 至 102 年 10 月 22 日	會議地點	英國利物浦
會議名稱	(中文) (英文)18th International Meeting of the European Society of Gynaecological Oncology		
發表題目	(中文) (英文) Predicting the Recurrent Factors of Cervical Cancer using C5, MARS and RF: a comparison study		

一、 參加會議經過

2013 年 18th International Meeting of the European Society of Gynaecological Oncology 年會在英國利物浦召開。本屆的年會為期 4 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 Glass with the Experts Sessions 以及 Tumour Board Sessions，目標針對現階段進行的子宮內膜癌症預後指標的研究議題與歐洲當地的研究工作者做互相討論，並獲得許多寶貴的經驗。同時大會將一些臨床技術發展的公司現場展覽可謂是一項與其他國際學術研討會最大與最有貢獻的特色。個人的發表論文題目為 “Predicting the Recurrent Factors of Cervical Cancer using C5, MARS and RF: a comparison study”，The Journal of Supportive Oncology 主編並針對個人研究展

示高度歡迎投稿。在議程的安排除了與以往相同有一些短期課程以外，大會將一些業界的職缺進行座談與謀合可謂是一項與其他國際學術研討會最大與最有貢獻的特色。

二、 與會心得

這是我第一次出席至歐洲參加國際學術研討會，尤其是參與歐洲婦女癌症學會(The European Society of Gynaecological Oncology, ESGO)年會，這一次學術的收穫豐富，更在會議會場中看見中華民國的國旗佇立飄揚(如下圖)，真是無比的興奮。值得一提的是，在會場中遇見長庚紀念醫院副院長張廷章教授，他剛好是子宮內膜癌症在台灣的首屈一指的專家，針對臺灣近年來，子宮內膜癌個案逐漸增多，可見其未來很可能會超過子宮頸癌、卵巢癌的趨勢交流彼此意見。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，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

Objectives

The choice of treatment for cervical cancer depends partly upon the risk of

recurrence. This is usually done using clinical judgement alone, and can be difficult. The objective of the present study was to identify the significant recurrent factors for cervical cancer. In addition, we developed C5, Multivariate Adaptive Regression Splines (MARS) and Random Forest (RF) model for predicting the recurrent factors.

Methods

To find out the recurrent factors, we first constructed a risk factor set through an extensive literature review of cervical. The cervical cancer dataset provided by the Chung Shan Medical University Hospital Tumor Registry is used in this study. Each patient in the dataset contains 12 predictor variables and the dependent variable is recurrence or no. We evaluated three models and compared their results using three statistical indices: accuracy, sensitivity and specificity.

Results

The findings revealed that Pathologic Stage, Pathologic T, Cell Type and RT target Summary were the most important prognostic factors, in contrast to other similar analysis (Grisaru et al., Cancer 97:1904-1908). The average correct classification rates / area under the curve of the C5.0, MARS and RF models are 0.924 / 0.889, 0.866 / 0.838 and 0.854 / 0.919, respectively.

Conclusions

Based on the findings, the C5.0 model not only generates the better classification result, but also can be used to select important independent variables for recurrent cervical cancer. For medical interpretation, we can develop some results by which a physician caring a patient can better decide when to take the critical intervention.

四、 建議

個人建議除了參與在美洲與亞洲會議的機會外，應當可以考慮出席在歐洲所主辦的各項癌症相關的重要年會。其優點在於歐洲學術的進步性不會比美洲遜色，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）18th International Meeting of the European Society of Gynaecological Oncology 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。

科技部補助計畫衍生研發成果推廣資料表

日期:2015/01/02

科技部補助計畫	計畫名稱: 子宮內膜癌症之創新臨床預後指標模式與醫療科技評估
	計畫主持人: 張啟昌
	計畫編號: 102-2633-E-040-001- 學門領域: 作業研究

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：張啟昌	計畫編號：102-2633-E-040-001-
計畫名稱：子宮內膜癌症之創新臨床預後指標模式與醫療科技評估	

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	1	1	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	0	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。)	臨床醫療決策有賴於多元實際證據的輔助分析。有鑑於過去的研究發展，文獻中臨床隨機試驗與非臨床隨機試驗設計所獲得預後指標的結論莫衷一是，對於子宮內膜癌的預後指標仍然無表法獲得一致性的結論。因此，本研究計畫藉由統合分析(meta analysis)的架構，並進一步延伸貝氏階層模式方法(Bayesian hierarchical model)，藉由文獻中臨床隨機試驗與非臨床隨機試驗設計加以整合分析，建立子宮內膜癌的預後指標模式並輔助臨床醫師施以個別化治療的策略。 本研究分別針對隨機臨床試驗使用 the modified Jadad scale；以及針對非隨機臨床隨試驗使用 the Newcastle–Ottawa Scale 方法。獲得結果之創新臨床預後指標模式為：PI=2.3×age+84 (if grade 2) or 135 (if grade 3)+69 (if stage Ib or Ic) or 127 (if stage II)+43 (if no lymphadenectomy)−57 (for adjuvant chemotherapy of 3 times or more)+24 (calibrating constant)。目前正針對本校附設醫院的癌症登記資料庫進行追溯研究分析。

	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）

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）

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臨床後續發展：本研究分別針對隨機臨床試驗使用 the modified Jadad scale；以及針對非隨機臨床隨試驗使用 the Newcastle–Ottawa Scale 方法。獲得結果之創新臨床預後指標模式為：PI=2.3×age+84 (if grade 2) or 135 (if grade 3)+69 (if stage Ib or Ic) or 127 (if stage II)+43 (if no lymphadenectomy)−57 (for adjuvant chemotherapy of 3 times or more)+24 (calibrating constant)。目前正針對本校附設醫院的癌症登記資料庫進行追溯研究分析。

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，子宮內膜癌雖尚未居於領先地位，但其數目也逐步上升，對於子宮頸癌的比率由五十年代的40:1(子宮內膜癌：子宮頸癌)，已在近年來增高為 14:1，故子宮內膜癌病例，在臺灣個案逐漸增多，可見其未來很可能會超過子宮頸癌、卵巢癌，成為本地區最常見的婦科癌症。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。