Steroids 104 (2015) 129–136

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Prognostic value of estrogen receptors mRNA expression in non-small cell lung cancer: A systematic review and meta-analysis

Wentao Li, Lap Ah Tse *, Feng Wang

JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region

ARTICLE INFO

Article history:
Received 12 June 2015
Received in revised form 31 August 2015
Accepted 18 September 2015
Available online 9 October 2015

Keywords:
Lung cancer
Survival
Estrogen receptor
Meta-analysis

ABSTRACT

The prognostic value of estrogen receptors (ESR1 and ESR2) mRNA expression in patients with non-small cell lung cancer (NSCLC) remains controversial. Therefore, a systematic review with meta-analysis was conducted. A systematic literature search was conducted in both Pubmed and Embase. Studies that reported association of ESR and survival in NSCLC patients in the form of hazard ratio (HR) and 95% confidence interval (CI) were included. Pooled HR was taken as the effect size to reflect the association. Five eligible articles provided six separate studies for ESR1 and four for ESR2. For ESR1, the pooled HR of overall survival was 0.72 (95% CI 0.41–1.27) by univariate analysis and was 0.33 (95% CI: 0.20–0.53) by multivariate analysis. For ESR2, the pooled HR was 0.95 (95% CI 0.73–1.23) by univariate analysis. Sub-group analysis suggested that the disease stages and cut-off point may explain heterogeneity among studies of ESR1. Results of the meta-analysis revealed a potential benefit of positive ESR1 mRNA expression in survival in patients with NSCLC, especially in those of advanced stage. No statistically significant association was found between ESR2 mRNA expression and NSCLC patients' prognosis.

1. Introduction

Globally, lung cancer has been the leading lethal cancer over centuries. Histologically, non-small cell lung cancer (NSCLC) accounts for approximate 87% of lung cancer [1]. Despite some breakthroughs in treatment research of lung cancer, the prognosis of NSCLC remains pessimistic, with a 5-year survival rate lower than 18.2% [1]. Targeted therapy has obtained increasing attention as it provided further treatment hope to the victims of NSCLC. EGFR (epidermal growth factor receptor) mutations and EML4-ALK (echinodermmicrotubule associated proteinlike 4-anaplasticlymphomakinase) translocations are two targets that have been successfully identified and targeted for the routine treatment in advanced stage patients[2,3]; however, they are deemed of limited application, as only a small fraction of NSCLC patients with certain defined tumor gene mutations are likely to respond well to the targeted treatment. This fact suggests that a large amount of NSCLC patients without certain defined mutations and all early to middle stages patients are not appropriate for targeted therapy. Thus, discovery of novel targets is in great demands for clinical oncological research.

Estrogen receptor (ESR), with two subtypes – ESR1 and ESR2, is a vital prognostic biomarker of breast cancer [4]. Recent studies showed that both ESR1 and ESR2 were expressed in the majority of human NSCLC cell lines, which provided credible evidence on possible links between sex hormones and NSCLC prognosis [5]. Moreover, a shorter survival was observed in post-menopausal women who received hormone replacement therapy comparing to those who did not [6], which might be a result of interactions among signaling pathways of ESR, EGFR and insulin-like growth factor-1 receptor [5,7].

The potential prognostic value of estrogen receptor mRNA expression in NSCLC survival remains elusive. Most ESR studies were conducted with relatively small number of NSCLC cases which led to their risk estimations unstable. A systematic review is going to be conducted with data synthesized when possible to evaluate the associations of expression of different types of estrogen receptors and prognosis in patients with NSCLC.

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; NSCLC, non-small cell lung cancer; ESR, estrogen receptor; OS, overall survival; PCR, polymerase chain reaction; IHC, immunohistochemistry.

* Corresponding author at: JC School of Public Health and Primary Care, The Chinese University of Hong Kong, 4/F School of Public Health and Primary Care, Prince of Wales Hospital, Sha Tin, N.T., Hong Kong Special Administrative Region.

E-mail addresses: waveofocean99@gmail.com (W. Li), shelly@cuhk.edu.hk (L.A. Tse).

http://dx.doi.org/10.1016/j.steroids.2015.09.005
0039-128X/

2. Experimental

2.1. Literature search strategy

Literature search was conducted in Pubmed and Embase. Electronically search was finished on February 15, 2015. Publication language was restricted to English. The search strategy employed was a combination of (a) estrogen receptor or ESR; (b) lung cancer, lung tumor, lung neoplasm or lung carcinoma; (c) survival, prognosis or mortality.

2.2. Eligibility of relevant studies

All searched studies were independently reviewed by two reviewers (WTL and LAT), discrepancies were solved by discussion with the third reviewer (FW). Pertinent studies were regarded as eligible if all the following criteria were fulfilled: (a) NSCLC cases with pathological diagnosis; (b) a cohort study design; (c) solid tumor as analytic samples; (d) polymerase chain reaction (PCR) was used to measure mRNA expression level of ESR1/ESR2; (e) survival analysis according to ESR1/ESR2 mRNA expression level for overall survival (OS); (f) hazard ratio (HR) and 95% confidence interval (CI) either provided or could be estimated from data provided in the primary studies. In case of overlapping of patients in different studies, only the one with the most extensive data was included. If results were presented in one article according to different subgroups, they were treated as separate studies.

2.3. Data extraction and quality assessment

Information extracted from each eligible study included ESR type, first author, publication year, number of participants, sex proportion, country or region of the cohort, cut-off point of ESR status in PCR analysis, histological type, stage, and HR with 95% CI (univariate and/or multivariate analysis). The European Lung Cancer Working Party quality scale for biological prognostic factors for lung cancer was applied to evaluate methodological quality of included studies [8]. Each included study was scored by two independent reviewers (WTL and LAT).

2.4. Statistical analysis

OS was taken as the primary outcome. HR was taken as the effect size to reflect the association between ESR1/ESR2 mRNA expression levels and patients' OS. For studies that did not report HR directly, estimation of univariate analysis results were conducted by a sequential well established procedure involves using the software Engauge Digitizer Version 4.1 and the Microsoft Excel software macro of survival analysis designed by J.F. Tierney [9]. This procedure has been widely employed in the meta-analysis of survival data [10].

Pooled HR was generated from meta-analysis. Positive ESR1/ESR2 mRNA expression was considered a better survival indication if pooled HR < 1 and its 95% CI did not contain 1. Heterogeneity between studies were measured by Q test and I^2 test. For Q test, $P < 0.10$ suggests significant heterogeneity. For I^2 test, $I^2 < 25\%$, between 25% and 50%, between 50% and 75%, and >75% respectively suggest low, moderate, high and extreme heterogeneity [11]. The fixed-effect model was conducted if no significant heterogeneity was detected; otherwise the random-effect model was carried out. Subgroup analysis was conducted to explore source of heterogeneity. Differences of effect sizes in small and large studies were explored by Beggs test. Sensitivity analysis was carried out by deleting one study each time to examine potential fluctuation of the pooled HR and its 95% CI. All statistical analyses were conducted by STATA 12.0 (Stata Corporation, College Station, Texas).

3. Results

There were no obvious discrepancies in terms of the judgments of eligibility and data extraction process. A total of five articles [12–16] that provided six separate studies for ESR1 and four for ESR2 were included in this review. A flowchart of the literature retrieval process was shown in Fig. 1.

3.1. Study characteristics

Characteristics of the six studies on ESR1 are shown in Table 1. All of them were published between 2010 and 2014. All studies employed quantitative reverse transcription PCR (qRT-PCR) to measure the expression of mRNA. Five of these studies were carried out in Europe and one was conducted in the USA. Four of them took the median levels of ESR1 mRNA expression as cut-off points to differentiate the positive ($\geqslant$median) and negative (<median) status [12–14], the other two studies considered the highest two tertiles as positive and the lowest tertile as negative status [16]. All included ESR1 studies directly reported unadjusted HRs and their 95% CIs, whilst only three of them provided adjusted HRs and their 95% CIs.

Table 2 summarized the main characteristics of the four studies on ESR2, which were published in 2010 or afterwards. Three of them were conducted in Europe and one was in the USA. Two of these studies employed the highest two tertiles as the positive and the lowest tertile as the negative status for the ESR2 mRNA expression [16]. One study took the median as the cut-off point [12] and another one did not give any description on selection of the cut-off point [15]. Three studies provided unadjusted HRs and their 95% CIs, all were obtained from the *K–M* curves, and one study reported the result without a clear description of analytic method, whilst none of them reported adjusted HR using multivariate analysis.

3.2. Quality assessment

Supplementary Table 1 shows the quality assessment scores for each study according to the European Lung Cancer Working Party quality scale for biological prognostic factors for lung cancer. In the domain of scientific design, all studies presented study objective and statistical methods clearly; however, none of them provided a description of preliminary assessment of sample size needed. Four studies were of prospective design and three were retrospective studies. Scores of the remaining domains vary among studies. For the methodology domain, four studies did not provide information on test of reproducibility. For the generalizability domain, all studies provided information on the selection criteria and patients characteristics to some extent, but information on treatment was inadequately described in four studies. For results analysis, only one study reported the number of events.

3.3. Prognostic role of ESR1 mRNA expression in NSCLC survival

Unadjusted HRs from all six studies were pooled into the meta-analysis (Fig. 2(A)), a total of 514 NSCLC cases were involved. Inconsistent HRs were observed among studies, indicating either positive or negative prognostic roles of ESR1. Random-effect model was employed to obtain an unadjusted pooled HR of 0.72 (95% CI 0.41–1.27, $I^2 = 73.7\%$, $P = 0.002$). Pooled adjusted HR was 0.33 (95% CI: 0.20–0.53, with 174 cases) by combining three studies