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Original Article

Female Gender Is an Independent Prognostic Factor in Non-small-cell Lung Cancer: A Meta-analysis

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Purpose: It is not clear whether women with non-small-cell lung cancer (NSCLC) live significantly longer than men. Thus, we conducted a meta-analysis of published studies to quantitatively compare NSCLC survival data between genders.
Materials and Methods: A MEDLINE Web search for computer-archived bibliographic data regarding overall survival differences between genders was performed. DerSimonian-Laird random effects analysis was used to estimate the pooled hazard ratio (HR).
Results: We selected 39 articles as appropriate data sources, involving 86 800 patients including 32 701 women and 54 099 men. Combined HRs for women vs. men in studies using univariate and multivariate analyses respectively were 0.79 ($p < 0.0001$) and 0.78 ($p < 0.0001$). Pooled HRs for 3 study subgroups having (1) fewer than 30% stage I cases, (2) fewer than 50% adenocarcinoma cases, and (3) statistical adjustment for smoking status all indicated the survival advantage of women.
Conclusion: This meta-analysis of published data concerning NSCLC patients indicated significantly better survival for women.

Keywords: non-small-cell lung cancer; thoracic surgery; gender; prognosis; meta-analysis

Introduction

Prognoses of lung cancer patients have been predicted reliably by disease stage.[1)] However, other candidate prognostic factors in addition to stage, also warrant consideration.[2)] One of the most important and fundamental biologic factors is gender. While a number of studies have reported that women with non-small-cell lung cancer (NSCLC) live significantly longer than men after surgical or non-surgical treatment,[3–6)] some other studies have shown no survival differences between genders. We, therefore, concluded that quantitative analysis combining data from multiple sources was necessary to resolve this issue.

Several confounding factors associated with gender may influence survival in NSCLC. One representative factor is a difference in smoking habits between genders. Smoking behavior is closely associated with social custom, and female/male smoking ratios are quite different between various regions and years of publication.[7, 8)] In general, female smokers are seen more frequently in Western than Eastern countries. According to geographic region, age-standardized incidence of lung cancer in women also varies worldwide, from 0.6 to 35.6 per 100000.[9)] This may be explained partially by regional differences in smoking habits among women.

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Because smoking may be the worst prognostic factor in lung cancer,[10, 11] differences in smoking habit prevalence could result in significant differences in survival outcome between genders.

Regarding histologic type of NSCLC, cigarette smoking is associated more closely with squamous cell carcinoma than with adenocarcinoma. This might be a major reason why adenocarcinoma, as opposed to squamous cell carcinoma, is found predominantly in women. Biologic features of adenocarcinomas in women, as represented by localized bronchioloalveolar carcinomas (BACs) showing low aggressiveness, may result in better prognoses.[12] Multiple previous studies[13–15] reported a survival advantage for women with resected NSCLC to be limited to patients with earlier disease stages or a nonsquamous histology. If this is so, the proportion of stage I and adenocarcinoma cases, and probably smoking status in the patients studied might affect comparisons of survival between genders.

In addition to these patient factors, statistical methods used to analyze survival differences, particularly univariate vs. multivariate, are important considerations when various confounding factors are present. In general, multivariate analysis is thought to be more reliable than univariate analysis under such circumstances.

We, therefore, conducted a meta-analysis of published studies of NSCLC that focused on survival differences between genders, aiming to quantitatively review the nature of survival advantages for female lung cancer patients, considering the aforementioned problems of disease stages, histologic types, smoking status, and analyzed statistical methods.

Materials and Methods

Eligibility criteria for the meta-analysis

This meta-analysis was limited to studies that compared overall survival data for women vs. men with NSCLCs. For a meta-analysis of time-to-event outcomes, the most appropriate statistic is the hazard ratio (HR).[16] Thus, HRs and associated 95% confidence intervals (CIs) reported in articles were used in the meta-analysis. The following eligibility criteria were established before assembling articles. (1) Articles were published in English in the periodical medical literature between January 1, 2000 and August 1, 2009. (2) Survival comparisons between genders for NSCLC patients were based on statistical analyses. (3) Summarized survival differences between genders were calculated from individual patient data and expressed explicitly as HR with its associated CI. (4) When multiple articles used the same data source, all data or a portion of it was used when the included patients did not overlap in the same meta-analysis. (5) Results of subgroup analyses in the same article were used when the included patients did not overlap in the same meta-analysis. (6) For articles based on the same data source with overlapping patients, the single most informative article was chosen for the meta-analysis.

Assemblage of published studies

A MEDLINE Web search for computer-archived bibliographic data regarding survival differences between genders with NSCLC was performed primarily on August 1, 2009. Key word searches for 'lung cancer + prognostic factor' and 'lung cancer + gender' provided 703 and 982 citations, respectively. Manual selection of relevant studies among these was based on summary analysis. Overlapping or unrelated articles were excluded, and items from hand-searched bibliographies were added. Of the 65 articles initially found by these methods, 26[13–15, 17–39] were excluded for reasons described in **Table 1**. Among the excluded studies, 18 showed results of univariate analyses, and the other 8 studies used multivariate analyses. While 9 excluded studies did not find significant survival differences between genders, 17 found significant survival benefits for women, including subgroup analyses. Among the 9 studies reporting no significant difference, 7 articles (78%) included women as fewer than 20% of patients, and/or fewer than 200 patients altogether. These small sample sizes probably limited the study's power to detect statistical significance.

We included 39 articles[40–78] in the present meta-analysis. In these patients, disease stages had been determined using the former international staging system[1] published in 1997. When percentages of adenocarcinoma for each study were calculated for the present study, BACs, which constituted a distinct category in pathologic classifications, were included among the adenocarcinomas.

Statistical analyses

DerSimonian-Laird random effects analysis[79] was used to estimate the pooled HR. Generally used to combine heterogeneous studies, this method produces a combined HR and a 95% CI. This is the simplest version of a random-effects meta-analysis; the standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of variation in different studies. The size of this adjustment can be estimated from the

Table 1 Articles excluded from the meta-analysis

Author (Year)	Patients	Women (%)	Stage	Statistics	Results	Reasons for exclusion
Minami (2000)	1242	27.1	I-IV	U	S (Survival analysis was limited to completely resected cases)	HR and CI not described
Jazieh (2000)	454	9.7	I-II	M	NS	HR and CI not described
Motohiro (2002)	799	25.9	I	U	S	SCLC included for survival analyses of genders
Jazieh (2002)	551	11.1	I-II	U	NS	HR and CI not described
Padilla (2002)	322	5.3	IB	U	NS	HR and CI not described
Alexiou (2002)	833	30.3	I-III	U	S (NS in stages higher than II in subgroup analyses)	HR and CI not described
Yoshino (2002)	1123	29.5	I-III	M	S	Same data source as Yano (2008)
Thomas (2002)	511	15.9	I	U	NS	HR and CI not described
Porrello (2002)	296	17.6	I	U	S	HR and CI not described
Kutlay (2003)	445	8.1	I-IV	U	NS	HR and CI not described; SCLC included
Sakao (2004)	65	36.9	IA	U	NS (DFS)	OS not described (DFS only)
Moore (2004)	7553	35.2	Local-Distant	M	S	Gender and histology were combined for survival analyses
Tammemagi (2004a)	1155	40.7	I-IV	U	S	SCLC included for survival analyses of genders
Tammemagi (2004b)	1155	40.7	I-IV	M	S	SCLC included for survival analyses of genders
Fu (2005)	228 572	35.8	Local-Distant	U	S	HR and CI not described; SCLC included
Ringer (2005)	2618	38.1	I-IV	U	S (Only in stage I)	HR and CI not described; SCLC included
Park (2006)	81	18.5	IB	U	S (DFS)	OS not described (DFS only)
Tsao (2006)	1370	39.6	III-IV	U	S (Only for chemotherapy; NS for chemoradiation therapy)	HR and CI not described
Cerfolio (2006)	1085	38.2	I-III	M	S (Significant in stages I to III in subgroup analyses)	HR and CI not described
Yoshino (2006)	428	46.5	I	M	NS	Same data source as Yano (2008)
Mizuno (2008)	106	39.6	IB	U	NS	HR and CI not described
Asamura (2008)	12 892	32.8	I-IV	U	S	HR and CI not described; SCLC included
Chiang (2008)	24 910	27.5	I-IV	M	S	SCLC included for survival analyses of genders
Chang (2009)	2770	39	I-IV	U	S (NS in non-adenocarcinoma and stages higher than II in subgroup analyses)	HR and CI not described
Jubelirer (2009)	2207	39.6	I-III	U	NS	HR and CI not described
Chansky (2009)	9137	25.6	I-IIIA	M	S	SCLC included for survival analyses of genders

M: multivariate analysis; U: univariate analysis; S: significant survival benefit for women; NS: not significant; SCLC: small cell lung cancer; OS: overall survival; DFS: disease free survival; HR: hazard ratio; CI: confidential interval

treatment effects and standard errors of the studies included in the meta-analysis. Heterogeneity among combined studies was tested simultaneously and indicated by Cochran Q values. A p value below 0.05 was considered to indicate significance. Evidence of publication bias was determined by the method of Egger et al.[80]; for this determination, a p value below 0.1 was considered to indicate significance. The statistical software used was StatsDirect, version 2.7.2.

Results

The 39 articles used as data sources for the present meta-analysis included 86800 patients: 32701 women (37.7%) and 54099 men (**Table 2**). The studies included were considered highly heterogeneous for multiple reasons. Percentages of adenocarcinoma in individual studies ranged from 17.3% to 100%.[51, 66, 67] Disease stages included varied from study to study; some studies analyzed only stage IA disease undergoing complete resection,[46, 53, 62, 65] while some others included only unresectable stage IIIB and IV patients scheduled for chemotherapy or chemoradiotherapy.[56, 59, 75] Final statistical analyses used either univariate or multivariate analyses, or both. In the multivariate analyses, covariates were selected differently among the individual studies, which might have increased the likelihood of heterogeneous study results.

With the aim of reducing the heterogeneity among studies, we initially divided them into 2 groups according to statistical methods used: univariate or multivariate analyses. When both analyses were performed in the same article, results of each were used in separate meta-analyses. From those studies using multivariate analyses, we further selected 3 study groups to conduct meta-analysis in order to reduce heterogeneity. We selected only multivariate analyses for further analyses, because they are more reliable than univariate analyses in managing the effects of confounding factors. The 3 selected groups were (1) studies that included fewer than 30% stage I patients, (2) studies that included fewer than 50% adenocarcinoma patients, and (3) studies using statistical adjustment to allow for the factor of smoking status.

In 11 studies with univariate analyses, the combined HR for women vs. men with NSCLC for overall survival was 0.79 (95% CI, 0.73 to 0.85; p <0.0001; **Fig. 1**); these combined studies were homogeneous (Q = 12.9, p = 0.226), while publication bias was absent (p = 0.350). In 38 studies with multivariate analyses, the combined HR was 0.78 (95% CI, 0.75 to 0.81; p <0.0001; **Fig. 2**); these combined studies were heterogeneous (Q = 82.4, p <0.001), and publication bias was present (p <0.001).

Among the multivariate analyses, 10 studies included fewer than 30% stage I patients. In this subgroup, the combined HR was 0.84 (95% CI, 0.81 to 0.88; p <0.0001; **Fig. 3**); these combined studies were homogeneous (Q = 8.36, p = 0.498), although publication bias was present (p <0.001). This result suggested that women survived longer than men, even in patient populations including advanced-stage disease, higher than stage I in more than 70% of patients.

In 11 studies with fewer than 50% adenocarcinoma patients, the combined HR was 0.77 (95% CI, 0.69 to 0.87; p <0.0001; **Fig. 4**); these combined studies were heterogeneous (Q = 29.1, p = 0.001), and publication bias was present (p = 0.01). This result suggested that the proportion of adenocarcinoma cases probably was not the decisive factor underlying the survival advantage for women.

Finally, in 11 studies that included adjustments for smoking status as one of the multivariate factors for survival analyses, the combined HR was 0.80 (95% CI, 0.76 to 0.85; p <0.0001, **Fig. 5**); these combined studies were homogeneous (Q = 12.2, p = 0.275), and publication bias was absent (p = 0.109). This result supported a conclusion that the survival advantage for women was independent of smoking habits.

Though inter-study heterogeneities and/or publication biases were detected in some sets of the above, combined studies, all analyses supported better survival for women than men with NSCLC.

Discussion

In the present meta-analysis, the summarized results of overall survival for women with NSCLC were significantly better than those for men in the sub-grouped studies extracted from the assembled articles. The most important question surrounding the finding has been whether the biologic behavior of these tumors differs between genders. Many previous studies have sought an answer for this question.

We first should take note of the differences in life expectancies between genders. In every country, without exception, women naturally live longer than men. If lung cancers all were in advanced stages and were similarly lethal for both genders, no need would exist to take life expectancy into consideration. However, if disease was similarly curable for both genders, overall survival after

Table 2 Articles included in the meta-analysis

Author (Year)	Patients	Women (%)	Stage	Stage I (%)	Adenocarcinoma (%)	Modality	Results
Ferguson (2000)	451	41.2	I-IV	46.8	48.1	Surgery	NS
de Perrot (2000)	1037	19.1	I-IV	46.3	35.4	Surgery	S
Keller (2002)	488	41.6	II-IIIA	0	65.2	Surgery + radiotherapy or surgery + chemoradiotherapy	NS (significant for non-squamous histology)
Battafarano (2002)	451	44.8	I	100	4.63	Surgery	NS
Ahrendt (2003)	188	42	I	56.4	50.0	Surgery	NS
Fernandes (2003)	284	35.6	I-IV	61.3	48.2	Surgery	S
Inoue (2004)	154	35.7	IIIA	0	65.6	Surgery	NS
Campione (2004)	224	16.5	IA	100	46.9	Surgery	NS
Chatkin (2004)	109	30.3	I	100	46.8	Surgery	S
Visbal (2004)*	4618**	41	I-IV	24.7	52.7	Various	S
Iizasa (2004)	402	36.6	I	100	60.9	Surgery	S
Nordquist (2004)	654	58.7	I-IV	22.0	100	Various	S
Batevik (2005)	351	32.2	I-IIIB	70.7	48.1	Surgery	S
Kawai (2005)	3082	39.6	IA	100	(about 73%)	Surgery	S
Martin (2005)	353	41.1	IIIA	0	58.6	Surgery	S
Goya (2005)	6611	30.4	I-IV	51.5	59.0	Surgery	S
Efficace (2006)	391	34.8	IIIB-IV	0	(about 78%)	Chemotherapy	NS (U) S (M)
Sun (2006)*	5018	41.6	I-IV	26.1	5.18	Various	S
ELCAP (2006)	269	58	ND	85.1	67.3	Surgery	S
Wakelee (2006)	1157	37.3	IIIB-IV	0	56.8	Chemotherapy	S
Vallbohmer (2006)	90	24.4	I-IIIA	50.0	36.7	Surgery	NS
Hanagiri (2007)	713	31.1	I-IV	63.8	60.4	Surgery	S
Ou (2007)	19 072	50.5	I	100	54.6	Surgery (most)	S
Wisnivesky (2007)	18 967	43.4	I-II	70.6	47.2	Various	S (subgroup analyses according to treatment)
Foegle (2007)	2028	9.7	ND	ND	23.8	Various	NS
Koike (2007)	3315	37.3	I	100	66.4	Surgery	S
Tsurutani (2007)	45	62.2	I-IV	35.6 (cI)	100 (BAC)	Various	S
Caldarella (2007)	2262	20.5	I-IIIB	10.4 (pNo)	17.3	Various	NS
Sawabata (2007)	103	27.2	I	100	65.0	Surgery	NS
Bryant (2007)	730	31.4	I-IV	45.9	43.3	Various	NS
Yano (2008)	1405	31.7	I-IV	63.1	59.8	Surgery	NS
Sculier (2008)	12426	21.4	I-IV	6.0	(about 58%)	Various	S
Chamogeorgakis (2008)	214	39.7	I-II	84.1	60.3	Surgery	NS
Asmis (2008)	1255	29.9	I-IV	ND	ND	Surgery + chemotherapy or chemotherapy	S
Chung-Ping Hsu (2009)	272	25.7	IB	100	52.2	Surgery	S
Teramukai (2009)	388	28.9	IIIB-IV	0	70.6	Chemotherapy	NS
McGovern (2009)	831	38.4	I-III	23.1	(about 62%)	Radiotherapy	S
Wang (2009)	315	34.9	I	100	37.5	Surgery	S
Li-Han Hsu (2009)	695	45.3	I-IV	8.9	69.8	Various	NS

M: multivariate analysis; U: univariate analysis; S: significant survival benefit for women; NS: not significant; ND: not described in the article; cI: clinical stage I; pN0: pathologic N0; BAC: bronchioloalveolar carcinoma

*Only results of subgroup analyses were used for overlapped patients in the same data source. **Excluded from total number

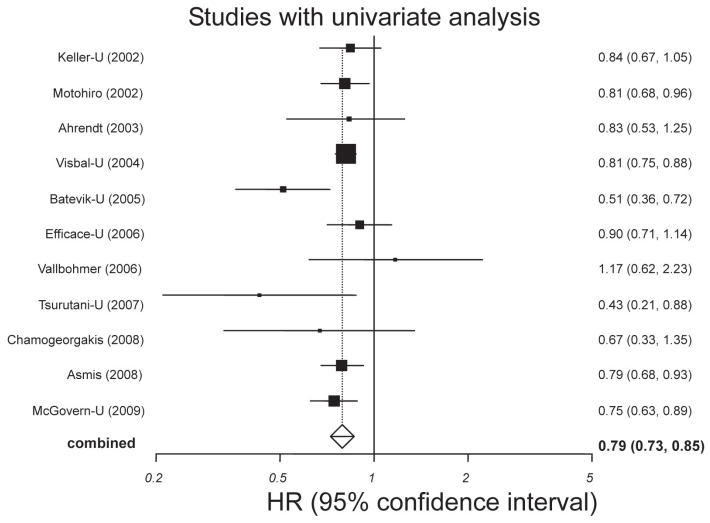

Fig. 1 Meta-analysis of hazard ratios (HR) of women compared to men on overall survival of non-small-cell lung cancer (NSCLC) patients in 11 studies using univariate analyses. Bars indicate the 95% confidence interval (CI) of the HR for women. Areas of squares are proportional to weights used in combining data. The center of the lozenge at the bottom presents the combined HR. A survival difference between genders was considered statistically significant if the 95% CI for combined HR did not overlap a value of 1.

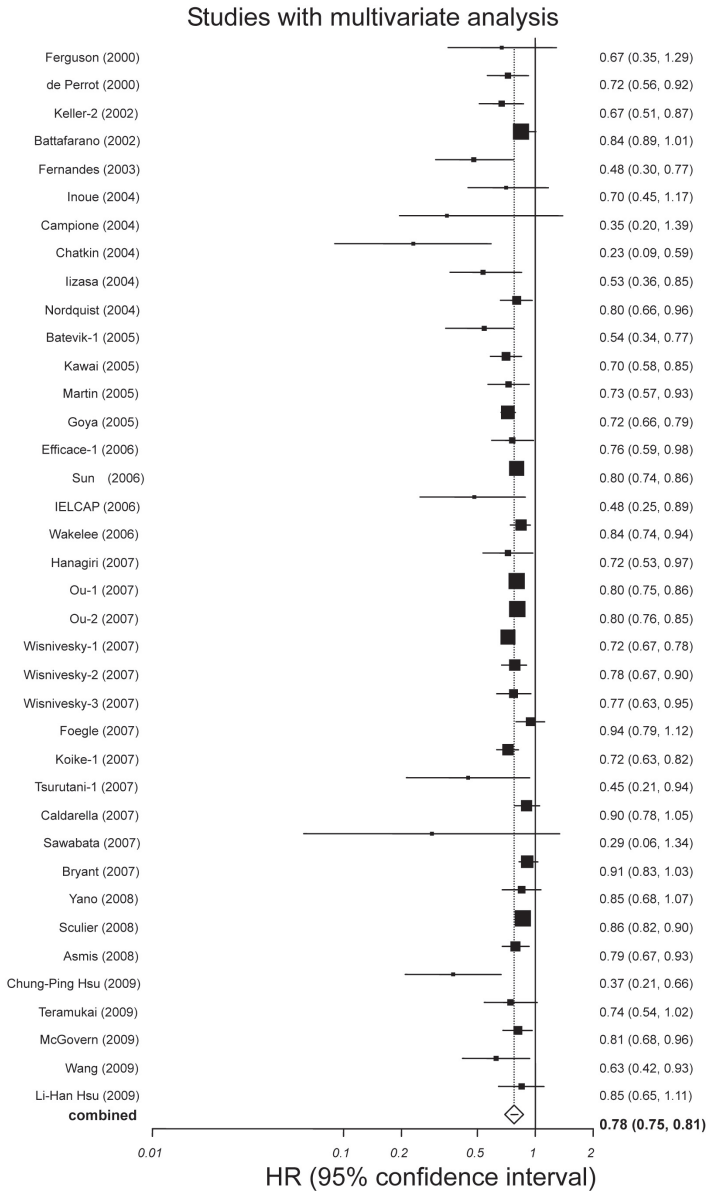

Fig. 2 Meta-analysis of hazard ratios (HR) of women compared to men concerning overall survival of non-small-cell lung cancer (NSCLC) patients in 38 studies using multivariate analyses.

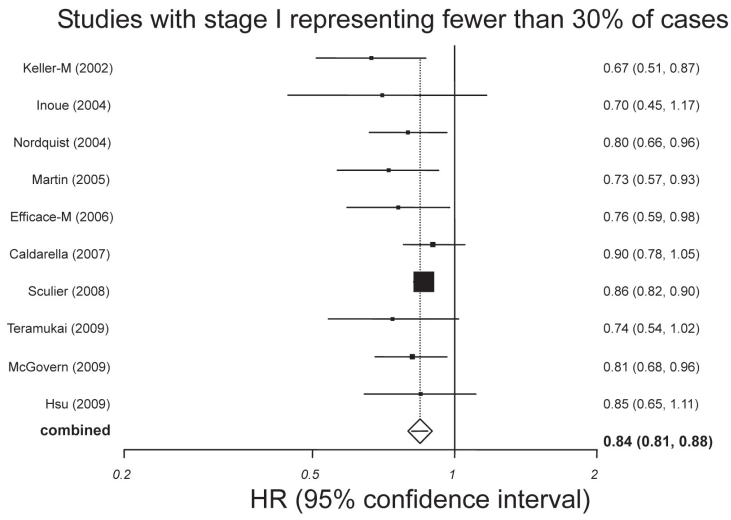

Fig. 3 Meta-analysis of hazard ratios (HR) of women compared to men concerning overall survival of non-small-cell lung cancer (NSCLC) patients in 10 studies including fewer than 30% stage I cases in the multivariate analysis.

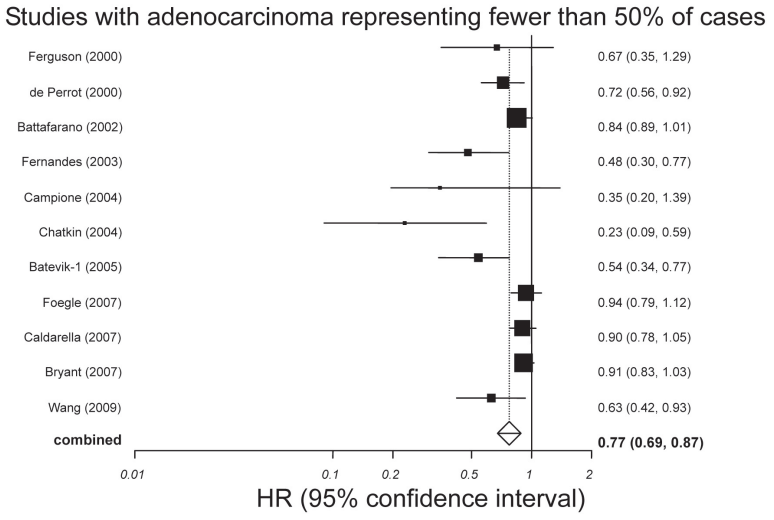

Fig. 4 Meta-analysis of hazard ratios (HR) of women compared to men concerning overall survival of non-small-cell lung cancer (NSCLC) patients in 11 studies including fewer than 50% adenocarcinoma cases in the multivariate analysis.

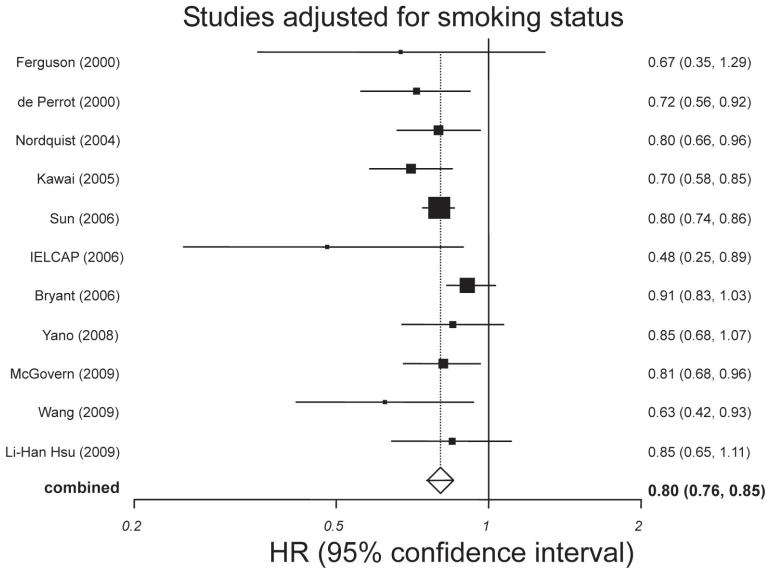

Fig. 5 Meta-analysis of hazard ratios (HR) of women compared to men concerning overall survival of non-small-cell lung cancer (NSCLC) patients in 11 studies using smoking status adjustments in the multivariate analysis.

treatment would depend on the normal life expectancy, which would always be longer for women. Focusing on this problem, Batevik et al.[52] compared survival differences between genders after resections of NSCLCs, and found that female gender had a positive impact on survival, irrespective of background life expectancy. Bouchardy et al.[81] also found a longer survival for women after adjusting for the effects of life expectancy. Although only 2 analyses have taken the longer life expectancy of women into consideration, those studies demonstrated that the survival advantage of women is not merely a reflection of a difference in natural background life expectancy. In addition to adjustment of life expectancy, difference of age at the onset of the disease is important for the exact analysis of survival difference. But, we could not find any reports describing on this point. Disease-free survival (DFS) might give some important information about the difference of biological behavior of the tumors in both genders. However, we could not perform meta-analysis concerning DFS, because only few reports had analysed DFS.

The relationships between gender survival differences and disease stages need to be clarified. Several studies[13, 14, 40, 41, 45, 76] reported that a survival advantage for women was confirmed only for resected stage I NSCLCs, which overall are highly curable. In contrast, Martin et al.[54] found a survival advantage for women with resected IIIA (N2) NSCLC patients who received preoperative chemotherapy. A large-scale international study reported that women had significantly better prognoses at all clinical stages,[71] not only the earlier ones. In addition, survival was longer for women in multiple randomized clinical trials that included chemotherapy for unresectable stage IIIB–IV NSCLCs.[32, 56, 59] These results suggest that overall, advanced stage NSCLCs in women respond to chemotherapy better than those in men. Our combined studies including fewer than 30% stage I patients in the present meta-analysis also demonstrated that survival for women was significantly better, implying that women's survival benefits were not limited to earlier disease stages.

Proportions of histologic types included in studies are likely to be important,[82] considering that some authors concluded that only women with adenocarcinomas show better prognoses. For example, Caldarella et al.[67] reported that, among women, survival was significantly better for adenocarcinoma patients than for those with squamous cell carcinoma. Keller et al.[42] also reported that, among patients who received adjuvant chemotherapy after resections for stage II and IIIA NSCLCs, a survival advantage for women was observed only for tumors with non-squamous histology. Chang et al.[15] confirmed a postoperative survival advantage for women only for stage I adenocarcinoma patients. However, when we combined studies including fewer than 50% of adenocarcinoma cases, the survival advantage for women was still significant. Since there seems to be few studies that analyzed survival versus histologic types among patients with NSCLC, additional, prospective studies are required to clarify this point.

A smoking habit is the strongest single patient-related factor affecting the prognoses of lung cancer patients, as well as the overall well-being of healthy people. As smokers have been predominantly men, one plausible reason to explain worse prognoses for men is that smoking promotes several life-threatening diseases, such as coronary ischemic disease, chronic obstructive pulmonary disease, pneumonia, and non-pulmonary malignant tumors. Hsu et al.[78] reported that median survival was the same for never-smoking women and never-smoking men with adenocarcinoma, suggesting that both smoking status and histologic type rather than gender decided survival. In several studies,[34, 40, 70] a significant survival advantage for women disappeared after statistically adjusting for smoking status, although in other studies[28, 41, 49, 51, 53, 57, 58, 76, 77] survival advantages for women persisted after adjustment for smoking. In our meta-analysis, which combined these conflicting studies, female gender still persisted as a favorable prognostic factor, independent of smoking status. Since heterogeneity and publication bias among the included studies were absent in this subgroup meta-analysis, better prognosis for women indeed would appear independent of tobacco smoking.

The reasons why women with NSCLCs live significantly longer than men remain elusive. The Japanese Joint Committee of Lung Cancer Registry performed 3 separate retrospective studies with 5-year follow-up periods for cases resected in the years 1989, 1994, and 1999. In these nationwide registry studies, women showed significantly better survival than men in every instance.[36] One plausible reason is increasing discovery of tiny adenocarcinomas developing in women. The number of computed tomography (CT) scanners per 1 million population was as high as 64 in Japan in 1996.[83] As a consequence, tiny peripheral lung cancers were discovered frequently. These well-differentiated adenocarcinomas were common among lung cancers that developed in women in

Japan. Most of these tumors grow more slowly and are less invasive than moderately and poorly differentiated adenocarcinomas, and show good postoperative survival. An Early Lung Cancer Action Program (ELCAP) clinical trial of CT screening[58] for early detection of lung cancer reported a higher detection rate in women than men (2.08% vs. 1.20%), and an HR for women as low as 0.48. Presumably, CT screening efficiently detected small peripheral adenocarcinomas in women, resulting in good outcomes. However, this cannot explain the result that women with lung cancer have better survival even in advanced stages, as shown in our meta-analysis.

Among recently-developed targeted molecular therapies, tyrosine kinase inhibitors of the epidermal growth factor receptor were shown to be effective for treating NSCLCs that harborspecific *EGFR* gene mutations. These tumor mutations develop frequently in specific subgroups of patients: those with adenocarcinomas, those who never smoke, women, and Asians.[84] Because prognoses differ between genders, the female/male ratio is important for comparing outcomes of surgery, drug therapy, or radiotherapy in clinical studies. We believe that gender differences in underlying molecular abnormalities in NSCLCs should be examined further to identify the unique biologic features of lung cancer in women.

In conclusion, our present meta-analysis of published data suggested that survival of women with NSCLC was significantly better than men, irrespective of statistical analyses used (univariate or multivariate), disease stages, histologic types, and smoking status. Since female gender is an independent prognostic factor in NSCLC as shown in this study, this prognostic difference should be taken into consideration, such as scrutinizing or standardizing the ratio of women to men in clinical trials, when we compare outcomes of various treatment modalities for NSCLC.

Conflict of Interest Statement

None declared.

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