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Mini-review

Lung cancer survival among never smokers☆

Ana Casal-Mouriño[a,b], Luis Valdés[a,c], Juan Miguel Barros-Dios[b,e], Alberto Ruano-Ravina[b,e,f,*]

[a] Neumology Department, Santiago de Compostable University Teaching Hospital, Spain
[b] Department of Preventive Medicine and Public Health, School of Medicine, University of Santiago de Compostela, Spain
[c] Interdisciplinary Neumology Research Group, Health Research Institute of Santiago de Compostela (Instituto Investigación Sanitaria de Santiago de Compostela/IDIS), Spain
[e] Consortium for Biomedical Research in Epidemiology & Public Health (CIBER en Epidemiología y Salud Pública /CIBERESP), Spain
[f] Department of Epidemiology, Brown School of Public Health, Brown University, Providence, Rhode Island, USA

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ABSTRACT

Lung cancer incidence among never smokers has increased in recent decades with 10–30% of all lung cancers occurring in never smokers, where exposure to residential radon is the leading cause of this disease. Lung cancer survival is low, ranging from 12% to 16% at 5 years of diagnosis. There is scant evidence to date on survival from this disease in never smokers. We aim to evaluate lung cancer survival in never smokers and ascertain whether there might be differences regarding smokers, through a systematic review applying predefined inclusion and exclusion criteria. 17 Studies were included. Never-smoker lung cancer patients seem to experience longer survival times than do smokers or ex-smokers. Lung cancer in never smokers displays distinctive clinical characteristics, is more frequent among women, is diagnosed at more advanced stages, and the predominant histologic type is adenocarcinoma. Further studies are necessary to ascertain lung cancer survival among never smokers.

1. Introduction

Lung cancer is an important Public Health problem, in that it is the leading cause of cancer-related death in the world, causing approximately 388,000 deaths in Europe annually [1]. In recent years, lung cancer mortality has decreased in both sexes, albeit more markedly in men, due to the late incorporation of women in the smoking habit [2]. Even so, there are countries, such as Spain, where female mortality continues to rise.

Smoking habit is the principal risk factor of lung cancer in 85% of cases [3]. Even so, incidence of lung cancer among never smokers has increased in recent decades, and currently around 10%–30% of all lung cancers occur in never smokers [4]. *A priori* this might seem a low percentage. However, if lung cancer in never smokers were to be regarded as a specific type of cancer, it could come to rank as the seventh leading cause of cancer-related death in the world [5]. Recent studies suggest that lung cancer in never smokers could be considered a different clinical entity to lung cancer in smokers, as the different mutational pattern in both tumor suppressor and driver genes would indicate [6]. Exposure to residential radon is the second leading cause of this disease in smokers and the leading cause in never smokers [7]. Other factors that have been linked to the appearance of lung cancer are passive smoking, occupation, diet, leisure-time activities, environmental pollution, and genetic susceptibility [8–11].

Lung cancer survival is low, ranging from 12% to 16% at 5 years of diagnosis [2,12]. This survival rate has hardly improved in recent years, so that early diagnosis, primary prevention, and improvements in treatment assume vital importance.

Bearing in mind the important Public Health problem posed by lung cancer and given that there is scant evidence to date on survival from this disease in never smokers, we sought to evaluate lung cancer survival in this subgroup of patients and ascertain whether there might be differences with respect to smokers. To this end, we conducted a systematic review of the scientific literature.

Abbreviations: PRISMA, Preferred reporting items for Systematic reviews and Meta-analyses; WHO, World Health Organization; EGFR, Epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ISEL, Iressa Survival Evaluation in Lung Cancer Study; ALK, Anaplastic lymphoma kinase; SEER, Surveillance Epidemiology and End Results

☆ This paper forms part of Ana Casal-Mouriño's doctoral thesis.

* Corresponding author. Dept of Preventive Medicine and Public Health, School of Medicine, C/San Francisco s/n, University of Santiago de Compostela, 15782, Santiago de Compostela, Spain.
E-mail address: alberto.ruano@usc.es (A. Ruano-Ravina).

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2. Materials and methods

2.1. Bibliographic search

We conducted a bibliographic search of Pubmed (Medline) and EMBASE using a predefined search strategy with a series of key words ("*lung neoplasms*", "*never smokers*", "*survival*"); in addition, we also searched the "*Cochrane Library*" database. To carry out the systematic review, we used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology [13]. The search covered the period 1 January 1995 through 1 January 2018, and was updated on 27 August 2018.

2.2. Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used to include papers in the systematic review: a) in terms of study design, we included cohort studies, case-control studies, systematic reviews and meta-analyses; b) in terms of population characteristics, we only included studies conducted on the general population; c) in terms of sample size, we included studies with more than 300 never-smoker patients with lung cancer; d) in terms of oncologic diagnosis, we only included cases with confirmed anatomopathologic diagnosis of lung cancer in at least 50% of cases; e) regarding follow-up, we included studies with a median or mean follow-up of one year or more; f) publications which did not differentiate smokers from never smokers in their results were excluded, and lastly, in terms of language, only studies in English and Spanish were included.

For the definition of never smoker, we used the World Health Organization (WHO) criteria, namely, any subject who has smoked fewer than 100 cigarettes in his/her lifetime or who has not smoked more than 1 cigarette per day over a period of 6 months. The remaining categories of smoking habit were classed as "ever-smokers" and were thus excluded from the study. Where never smokers were defined without any concrete definition in the studies located, the study was included: in all such cases, however, we took into account the fact that such subjects might have been indicated as "never smokers" rather than as "nonsmokers". This lack of information was penalized on the quality scale used to assess the papers included (see below).

The results of each study were summarized in a table and the overall qualitative response obtained was reported in the text. We were unable to perform a meta-analysis due to the marked heterogeneity of the studies included.

2.3. Assessment of the quality of the studies included

The full text of the studies included was reviewed by two authors, with any discrepancies in the interpretation of any given paper being settled by consensus. A quality scale was developed for allowing to compare the quality of the manuscripts included in the review and it is described in Table 1. Without such a scale a reader could give the same importance to a paper with a low sample size, short follow-up, and unclear never-smoking definition compared to a research with high sample size, long follow up and clear definition of a never smoker. Regarding the items considered, a higher score was given for investigations with higher sample sizes, a higher score was given if the research was performed in more than one hospital in order to award a potential higher external validity. Regarding histologic confirmation, a higher score was given when more patients had this confirmation type because it reduces the risk of lung cancer misclassification. Regarding the recruitment period, a higher score was given when this period was lower because this is a way to consider centres with a higher annual number of cases. Finally, for the definition of never smokers, we gave a higher score to those studies clearly using the WHO definition, which avoids the possibility of misclassify ex-smokers with never-smokers. A different weight was assigned to each characteristic of these variables, which enabled us to create a continuous scale from 0 to 10 points. Table 1.

Table 1
Quality scale used to evaluate the studies included.

Item evaluated	Characteristic	Weight
Sample size	300–499	0
	500–800	1
	≥801	2
Setting	Single-center	0
	Multicenter	2
Histologic confirmation	< 90%	0
	≥90%	2
Enrolment period	< 5 years	2
	≥5 years	0
Smoking habit	No data	0
	WHO definition	2
TOTAL		10

3. Results

3.1. Search results

A total of 687 papers were retrieved. After having read all the abstracts, we selected 234 for full-text review. Of these, 17 were judged to fulfill the above inclusion criteria and included in the systematic review. Most of these studies had been conducted in North America and China. The sample size of the papers included ranged from 318 to 2,319 never-smoker subjects. The most frequent exclusion criteria were insufficient sample size and a lack of analysis of results in the specific subgroup of never smokers. A description of the search process is given in Fig. 1.

3.2. Results of the studies included

The studies published to date that scored highest on the quality scale were those of *Viñolas* et al. and *Wu* et al. Tables 2–4 show a description of all papers included in the systematic review.

Viñolas et al [14] conducted a prospective multicenter epidemiologic study which included 804 Spanish women never smokers and 1231 controls (smokers or ex-smokers). The most frequent histologic type among women never smokers was adenocarcinoma (83.4%; 62.1% in stage IV), in which there was a higher percentage of mutations in epidermal growth factor receptor (EGFR) as compared with smokers (46.9% *vs.* 19%). Mean overall survival among women never smokers with mutated EGFR, unmutated EGFR and indeterminate EGFR mutation was 25.6 (22.0–29.1), 16.2 (13.5–18.9), and 18.1 (11.6–24.6) months respectively. Survival of those patients receiving treatment with tyrosin-kinase inhibitors was 23 months (95%CI 19.9–26.1).

In 2017 ***Cho et al*** [15] published a retrospective study that included 707 Korean, never-smoker, lung cancer patients and 1153 smokers or ex-smokers. The most frequent lung cancer among never smokers was adenocarcinoma (89.8%; 39.2% in stage IV). "Never-smoker" status was associated with longer survival (overall survival rate at two years of 75.8% vs. 49.8% in smokers -$p < 0.001$). Overall survival for patients with EGFR mutations was higher in never smokers compared to smokers. In patients with squamous lung cancer survival was higher in smokers compared to never-smokers. ***Fang et al*** [16] conducted a study in which they evaluated 404 Chinese women never smokers with lung cancer. Mean survival in the never-smoker subgroup was 23.49 months. In 2017, ***Xie et al*** [17] published a retrospective study aimed at evaluating the effect of body mass index on patients undergoing surgical resection for stage-I non-small cell lung cancer (NSCLC), and showed that excess weight was associated with better prognosis. This study included 318 never-smoker patients, among whom the most frequent histologic type was adenocarcinoma (65.1%). In the subanalysis of

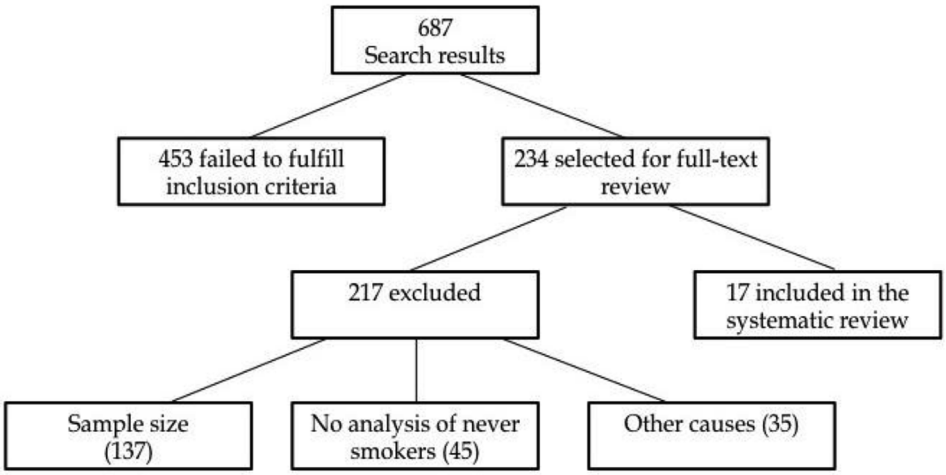

Fig. 1. Flowchart showing the inclusion and exclusion of studies.

never-smoker patients, the overall survival rate was 94.1 ± 1.3% and 86.4 ± 2% at 3 and 5 years, respectively.

Zheng et al [18] conducted a retrospective study on 1164 never-smoker patients with NSCLC, with the aim of evaluating their clinicopathologic and prognostic characteristics. They found greater disease-free progression (67 vs. 38 months; log rank: $p < 0.001$) and overall survival among never smokers as compared with smokers. Ex-smokers with EGFR mutations had a higher survival compared to non mutated ex-smokers. ***Dhillon*** [19] published a review article on the efficacy and tolerability of Gefitinib in locally advanced or metastatic NSCLC with EGFR mutations. In this review, they show the results of the Iressa Survival Evaluation in Lung Cancer study [20] (ISEL: a randomized clinical trial in phase III that compared Gefitinib with placebo), in which the 375 never-smoker patients included had a mean overall survival of 8.9 months. Average survival for patients on Gefitinib treatment was 6.3 months.

Parente-Lamelas et al [21] carried out an observational, retrospective, single-center study that included 396 never-smoker patients with lung cancer and 1765 smokers. Whereas mean survival at 5 years in the subgroup of never smokers, was 12.4% (median survival: 7.7 months; 95% CI: 9.29–16.5), the equivalent figure among smokers was 8.69% (median survival: 7.9 months; 95% CI: 7.37–10.26), without any statistically significant differences between the two groups (log rank: 2.47; p = 0.11). ***Wu et al*** [22] conducted a meta-analysis which included a total of 1876 never-smoker patients with NSCLC. They evaluated the association between certain genetic mutations and lung cancer survival among never smokers. The *loci* evaluated resulted in a mean reduction of 5–8 months in survival time. On performing a retrospective analysis of survival in a case series that included a total of 393 never smokers, ***Kim et al*** [23] found evidence to show that lower age, earlier stage at diagnosis, presence of bronchoalveolar carcinoma, mutation in EGFR, and never-smoker status (HR 2,374; 95% CI: 1496-3,769; $p = 0.000$) implied greater survival. 5-year survival was higher for patients with EGFR mutations compared to patients not presenting such mutations (56 vs 40%). This survival increased to a 63% when patients received treatment with tyrosin-kinase inhibitors (63%). ***Ferketich et al*** [24] analyzed the results of the US "NSCLC Database Project", which included 616 never-smoker subjects (82% adenocarcinomas, 56% in stage IV). Mean survival of never-smoker stage-III and -IV patients was 37.3 and 19.6 months, respectively. When ***Pu et al*** [25] analyzed the results of 722 never-smoker patients with NSCLC (MD Anderson Cancer Center and Mayo Clinic), they found the mean survival times to be 23.2 months for the MD Anderson patients and 44.6 months for the Mayo Clinic patients. The reason for this difference was that the Mayo Clinic patient population presented with an earlier stage at diagnosis, which enabled them to undergo surgery.

In their study, ***Johnson et al*** [26] specifically analyzed the survival of 344 US never smokers with advanced pulmonary adenocarcinoma, obtaining a mean survival time of 30.4 (25.3–32.6) months. Patients with EGFR mutations showed a higher survival compared to those without such mutations. In 2012, ***Han at al*** [27] published the results of a randomized clinical trial in phase III which included 313 Korean never smokers with stage-IIIB or -IV pulmonary adenocarcinoma. They obtained a mean survival time of 22.3 and 22.9 months for patients treated with Gefitinib and Gemcitabine, respectively. Mean survival for patients with EGFR mutations treated with gefininib and Gemcitabine was 27.2 and 25.6 months, respectively. ***Gómez et al*** [28] conducted a case-control study on 462 women never smokers with lung cancer (81.82% adenocarcinomas, 46.97% in stage IV). The five-year survival rate in the subgroup of never smokers ranged between 25 and 40%. ***Ahn et al*** [29] analyzed the survival of 2,319 never-smoker patients with lung cancer drawn from two registries (Korean and US): the mean survival time of these patients was 18 and 11 months, respectively. Mean survival was higher for adenocarcinoma compared to squamous lung cancer for both Korea and US. In 2011, ***Janjigian et al*** [30] published a cohort study that included 331 never-smoker patients with stage-IIIB and IV lung cancer (69% adenocarcinomas, 4% epidermoid carcinoma, 27% NSCLC). Patients who had never smoked registered a longer mean survival (17.8 months) than did smokers (11.3 months). In their cohort study, ***Hsu et al*** [31] included 382 never-smoker patients with lung cancer (94.5% adenocarcinomas). Their results show the same mean survival time for both men and women never smokers with adenocarcinoma (22.83 months). Survival was shorter for squamous lung cancer (15.7 months).

3.3. Quality of the studies included

The quality scale scores for the papers reviewed ranged from 2 to 8 points, with the best quality being obtained by the studies of ***Viñolas et al*** [14] and ***Wu et*** al, [22] with 804 and 1,876 never-smoker patients, respectively. The average score of the studies included was 5.24 points.

4. Discussion

This is the first systematic review to focus on analyzing lung cancer survival among never smokers. The studies published suggest better survival among never smokers versus smokers or ex-smokers, though some papers failed to find significant differences between the two groups. Considering the frequency of the disease, the low number of studies in the literature specifically aimed at ascertaining lung cancer survival among never smokers is noteworthy, and is in sharp contrast to the high number of studies published on ever-smokers.

Table 2
Description of the studies included.

Author	Study design	Number of never smokers and recruitment period	Mean age (years) and % women	Passive exposure to tobacco smoke	Most frequent histologic type	% Cases with mutated EGFR	Most frequent stage (% cases)	Survival results (never smokers)	Survival results (smokers)	Score
Viñolas et al. [14]	Multicenter epidemiologic study (Spain)	804 - 5 years (October 2007–December 2012)	68.4 (67.6–69.2) - 100%	38.3%	Adenocarcinoma (83.4%)	46.9%	IV (62.1%)	Mutated EGFR: 25.6 m (22–29.1) Wild-type EGFR: 16.2 m (13.5–18.9) Indeterminate: 18.1 m (11.6–24.6)	Mutated EGFR: Wild-type EGFR: 13,1 m (10,8–15,5) Indeterminate:	8
Cho et al. [15]	Retrospective single-center study (Korea)	707 - 3 years (June 2011–December 2014)	65 - 83.7%	-	Adenocarcinoma (89.8%)	57.8%	IV (39.2%)	Overall survival rate at 2 years: 75.8%	Overall survival rate at 2 years: 49.8% Mean overall survival: 23,9 m (19,9–27)	7
Fang et al. [16]	Case-control –two-center study (China)	402 - 3 years (March 2010–May 2013)	56.45 ± 11.45 - 100%	-	Adenocarcinoma (80.1%)	-	-	Time of mean survival: 23.49 m	-	6
Xie et al. [17]	Single-center cohort study (China)	318 - 5 years (December 2005–December 2010)	54.3% ≥ 60 years - 34.6%	-	Adenocarcinoma (65.1%)	-	Only includes stage I	Overall survival rate at 3 years: 94.1 ± 1.3%; at 5 years: 86.4 ± 2%	Overall survival rate at 3 years: 83,4 ± 2,2%; at 5 years: 75,1 ± 2,6%	2
Zheng et al. [18]	Retrospective single-center study (China)	1164 - 6 years (October 2007–May 2013)	59.1 (22–84) - 76.5%	-	Adenocarcinoma (87.3%)	67.9%	I (60.1%)	Five year survival rate: 75%	Five year survival rate: 70%	6
Dhillon [19] –Tatcher et al. [20]	Review paper – Multicenter randomized phase-III clinical trial (Europe, Asia, America, Australia, Canada)	375 - 1 year (2004)	Cases: 62 (28–90) Controls: 61 (31–87) - Cases: 33% Controls: 33%	-	Cases: Adenocarcinoma (45%) Controls: Adenocarcinoma (45%)	-	Cases: IV (47%) Controls: IV (50%)	Time of mean overall survival: 8.9 m	Time of mean overall survival: 5 m	6
Parente-Lamelas et al. [21]	Retrospective observational single-center study (Spain)	396 - 12 years (January 1999–December 2011)	72.85 ± 10.52 - 64.6%	-	Adenocarcinoma (55.6%)	-	IV (61.4%)	Time of mean overall survival: 7.7 m (95% CI: 9,29–16,5)	Time of mean overall survival: 7.9 m (95% CI: 7.37–10.26)	2
Wu et al. [22]	Meta-analysis –multicenter- (China, USA)	1876 - MD Anderson: 13 years (1995–2008) Mayo Clinic: 10 years (1997–2007) Taiwan: 8 years (2002–2010)	61.2 - 72.83%	-	Adenocarcinoma (77.87%)	-	IV (45.47%)	MD Anderson: mean survival: 26.7 m (mutated) vs. 13.66 m (unmutated) Mayo Clinic: mean survival 36 m (mutated) vs. 24.58 m (unmutated) Taiwan: mean survival 29.26 m (mutated) vs. 24.76 m (unmutated)	.	**8**
Kim et al. [23]	Retrospective – single-center case series (Korea)	393 - 12 years (June 1998–February 2010)	EGFR absent: 63.9 ± 9.7 Mutated EGFR: 61.8 ± 9.7 - EGFR absent: 37.9% Mutated EGFR 62.1%	-	EGFR absent: 45.6% adenocarcinoma Mutated EGFR: 54.4% adenocarcinoma	41.02%	EGFR absent: II (75.5%) Mutated EGFR: I (46%)	Five year survival rate: 60%	Five year survival rate: 30%	2

(*continued on next page*)

Table 2 (*continued*)

Author	Study design	Number of never smokers and recruitment period	Mean age (years) and % women	Passive exposure to tobacco smoke	Most frequent histologic type	% Cases with mutated EGFR	Most frequent stage (% cases)	Survival results (never smokers)	Survival results (smokers)	Score
Ferketich et al. [24]	NSCLC database -multicenter (USA)	618 - 4 years (January 2007–December 2011)	61.3 ± 13.1–65.70%	-	Adenocarcinoma (82%)	-	IV (56%)	Time of mean survival, stage III: 37.3 m Time of mean survival, stage IV: 19.6 m	Time of mean survival, stage III: 20,1 m Time of mean survival, stage IV: 6,7 m	7
Pu et al. [25]	Multicenter (USA)	722 - 11 years (1997–2008)	MD Anderson: 61.5 Mayo Clinic: 61.7 -MD Anderson: 67% Mayo Clinic: 73%	-	MD Anderson: adenocarcinoma (77%) Mayo Clinic: adenocarcinoma (68%)	-	MD Anderson: IV (52%) Mayo Clinic: I (34%)	MD Anderson: time of mean survival: 23.2 m Mayo Clinic: time of mean survival: 44.6 m	-	7
Johnson et al. [26]	Retrospective –single-center review (USA)	344 - 7 years (2002–2009)	65 (25–92) − 59%	-	Adenocarcinoma (100%)	27%	IV (100%)	Mean survival time: 30.4 m (25.3–32.6)	Mean survival time: 22.1 m (19.0–25.5)	4
Han et al. [27]	Multicenter randomized clinical trial phase-III (Korea)	309 - 2 years (October 2005–November 2007)	Gefitinib: 57 (32–64) Gemcitabine: 56.5 (19–74) -Gefitinib: 88% Gemcitabine: 89.3%	-	Adenocarcinoma (100%)	Gefitinib: 16.3% Gemcitabine: 10.7%	Gefitinib: IV (89.3%) Gemcitabine: 90.7%	Gefitinib: mean survival time 22.3 m Gemcitabine: mean survival time 22.9 m	-	6
Gómez et al. [28]	Multicenter- case-control (USA)	462 - 8 years: Phase I (September 1998–March 2003) Phase II (July 2005–March 2008)	67.34 - 100%	64.07%	Adenocarcinoma (81.82%)	-	IV (46.97%)	Five year survival rate: 25–40%	-	4
Ahn et al. [29]	Retrospective –single-center review (Korea, USA)	2319 - 7 years (1998–2005)	Korea: 61 (38–77) USA: 75 (46–89) -Korea: 65.9% USA: 62.9%	-	Korea: adenocarcinoma (66.6%) USA: adenocarcinoma (50.5%)	-	IV (46.2%)	Korea: mean survival time: 18 m USA: mean survival time: 11 m	Korea: mean survival time: 14 m USA: mean survival time: 9 m	6
Janjigian et al. [30]	Prospective –single-center- cohort study (USA)	331 - 3 years (June 2003–March 2006)	59 (24–93) − 66%	-	Adenocarcinoma (69%)	-	IV (80%)	Mean survival time: 17.8 m	Mean survival time: 11.3 m - ≤ 15 pack year history: 14.6 m - > 15 pack year history: 10.8 m	4
Hsu et al. [31]	Prospective –single-center- cohort study (China)	382 - 3 years (January 2002–December 2005)	Women: 59.5 Men: 65–45.32%	-	Never smokers: adenocarcinoma (94.5%)	-	Women: IV (53.9%) Men: IV (51.8%)	Women with adenocarcinomas: mean survival time: 22.83 m Men with adenocarcinomas: mean survival time: 22.83 m	Women with adenocarcinomas: mean survival time: 20.3 m Men with adenocarcinomas: mean survival time: 16.4 m	4

Table 3
Survival results regarding EGFR mutation and tyrosine-kinase inhibitors use.

Author	Number of patients with EGFR mutations	Survival results (EGFR mutations)	Survival results (tyrosine-kinase inhibitors)
Viñolas et al. [14]	Smokers: 83 Never smokers: 231	25,6 m (22.0–29.1) Chemotherapy: 26.7 m (16.1–37.3)	23 m (19.9–26.1)
Cho et al. [15]	Smokers: 164 Never smokers: 353	Smokers: HR 0.52 (95% CI: 0.3–0.7) Never smokers: HR 0.46 (95% CI: 0.4–0.8)	-
Zheng et al. [18]	Smokers: 204 Never smokers: 698	Former Smokers OS: HR 0.3 (95% CI: 0.1–0.7)	-
Dhillon [19] –Tatcher et al. [20]	26	Not shown	Gefitinib: 6.3 m
Kim et al. [23]	354	Five year survival rate: - EGFR mutation: 56% - EGFR absent: 40%	Five year survival rate: - EGFR TKIs: 63%
Johnson et al. [26]	275	33,7 m (31.6–39)	-
Han et al. [27]	42	EGFR mutation: Gefitinib: mean survival time 27.2 EGFR mutation: Gemcitabine: mean survival time 25.6	22.3 m

In our systematic review, the studies of ***Viñolas et al*** [14] and ***Wu et al*** [22] were ranked as having the best quality (8 points each). Generically speaking, the data reviewed show that lung cancer in never smokers is more frequent among women (34.6%–100%), with the most prevalent histologic type being adenocarcinoma (45%–94.5%) in stage IV (39.2%–90.7%), with EGFR mutations (10.7%–67.9%). In this subgroup of never-smoker patients, the mean overall survival reported in the studies ranged from 7.7 to 44.6 months. Despite that few studies show survival by histologic type, a higher survival is observed for adenocarcinoma (mean overall survival ranged from 5.4 to 30.4 months) compared to squamous lung cancer (11–21 months). Survival is even higher in patients with EGFR mutations (25.6–33.7 months) or for those receiving treatment with tyrosin-kinease inhibitors (5-year survival 63% compared to 40% in non-mutated patients) [23]. In this regard, however, note should be taken of the marked heterogeneity of the studies included.

Certain genetic and molecular factors have been linked to histologic differences lung cancer in never smokers, basically associated with the most frequent histologic type in lung cancer, i.e., adenocarcinoma [32]. This aspect hinders interpretation of the results obtained in our review, given that the most recent studies differentiate survival among never smokers according to whether or not they harbor the driver-gene mutations which improve the clinical results of such patients. Most of these studies do not report the results on overall survival among never smokers. EGFR mutations are more frequent in adenocarcinomas, women, and never-smoker patients [32,33]. *Gaughan* et al. [34] describe a higher frequency of family history of lung cancer in never smokers with NSCLC, and particularly among those who present with EGFR mutations. Never-smoker patients have also been observed to have specific mutations of the K-ras oncogene with a greater number of guanine-adenosine transitions in codons 12 and 13 [35]. Similarly, anaplastic lymphoma kinase (ALK) gene rearrangements occur more often in never smokers [36]. In patients with advanced or metastatic disease, identification of these molecular mutations is of vital importance when it comes to being able to administer specific treatments, though there tends to be more limited evidence for stages I-III.

Furthermore, the difference between never-smokers and smokers in terms of stage at diagnosis is not entirely clear. It has been postulated that never-smoker subjects are diagnosed at more advanced stages, possibly explained by the higher probability of lung cancer in smokers than in nonsmokers. This possibility might translate as a tendency toward lower survival rates among never smokers due to a higher presence of advanced stages.

Another difficulty observed in our review lies in the heterogeneity of endpoints used. Hence, while some studies use mean and others use median survival, there are still others that use survival at one or at two

Table 4
Survival results for squamous cell carcinomas *vs* adenocarcinomas.

Author	Number of squamous cell carcinomas	Number of adenocarcinomas	Survival results (squamous cell carcinomas)	Survival results (adenocarcinomas)
Viñolas et al. [14]	Smokers: 151 Never smokers: 43	Smokers: 670 Never smokers: 645	-	Wild type: 16.2 m (13.5–18,9) Not recorded: 18.1 m (11.6–24.6)
Cho et al. [15]	Smokers: 483 Never smokers: 25	Smokers: 518 Never smokers: 635	Smokers: HR 1.3 (95% CI: 1.0–1.6) Never smokers: HR 2.3 (95% CI: 1.1–4.5)	Smokers: HR 1 Never smokers: HR 1
Zheng et al. [18]	Smokers: 530 Never smokers: 100	Smokers: 476 Never smokers: 1016	Former Smokers OS: HR 0.97 (95% CI: 0.3–3.3)	-
Johnson et al. [26]	-	1036	-	Mean survival time: 30.4 m (25.3–32.6)
Han et al. [27]	-	313	-	Mean survival time: 22.9 m
Ahn et al. [29]	3446	5893	**1998–2001:** - Korean mean survival time: 15 m (13–17) - US mean survival time: 11 m (10–12) **2002–2005:** - Korean mean survival time: 21 m (18–23) - US mean survival time: 12 m (10–13)	**1998–2001:** - Korean mean survival time: 11 m (10–12) - US mean survival time: 11 m (10–12) **2002–2005:** - Korean mean survival time: 20 m (18–23) - US mean survival time: 12 m (10–13)
Hsu et al. [31]	87	485	Mean survival time: 15,7 m	**Never smokers:** Women's mean survival time: 22.83 m Men's mean survival time: 22.83 m **Smokers:** Women's mean survival time: 20.3 m Men's mean survival time: 16.4 m

years, and there are very few studies that have analyzed survival at five years of diagnosis. This renders interpretation and comparison of survival results extremely difficult. For instance, median survival figures tend to be lower than mean survival figures (and are more robust indicators), and the use of mean survival figures may give an optimistic view of survival. These differences also hinder comparison of results with those of smokers. This is compounded by the fact that the US Surveillance, Epidemiology, and End Results (SEER) program, which pools survival data from all lung cancers registered in the USA, does not include data on smoking habit, something that would allow for a good picture to be formed of lung cancer survival in never smokers.

This review can claim some advantages. Firstly, it is a systematic review, so that the likelihood of not having included relevant information is negligible, given the comprehensiveness of the search strategy. Furthermore, an effort was made not to miss any information, and proof of this is the high number of papers submitted to a full-text review (close on 250 studies). Moreover, the same type of information was evaluated in each of the studies included, and the results were separately assessed by two authors. We feel that the external validity of our review is acceptable, in view of the fact that the studies included populations from different geographical areas with a specific environmental exposure. Lastly, a quality scale was purpose-designed to evaluate the studies included, recording an average score of 5.24 points (score range 2–8 points). The studies under review included a considerable number of never-smoker patients, though always less than that of smoker or ex-smoker patients.

On the other hand, our review also has some limitations, the principal of which is the marked heterogeneity in the methodology of the studies included. Indeed, this was the main reason for being unable to perform a meta-analysis, whose results would have allowed us to establish more robust conclusions. After the full-text review, many papers had to be excluded for specifically failing to furnish survival figures for never-smoker patients. In addition, some of the papers only included specific subgroups of never-smoker patients with lung cancer (only women, only adenocarcinomas, or only stages IIIB-IV), thereby making extrapolation of the results for the rest of never-smoker patients difficult. Similarly, only two of the papers [14–28] evaluated passive exposure to tobacco smoke both in the home and the workplace, a finding which we feel should be borne in mind when it comes to interpreting the results. None of the studies considered exposure to residential radon among never smokers.

In conclusion, never-smoker lung cancer patients seem to experience longer survival times than do smokers or ex-smokers. Lung cancer among never smokers displays distinctive clinical characteristics, is more frequent among women, is diagnosed at more advanced stages, and the predominant histologic type is adenocarcinoma.

The design of future studies should include higher sample sizes of never-smokers analysing survival by subgroups (histological type, mutations in driver genes for lung cancer, or exposure to occupational carcinogens or radon). A currently unanswered question is if the diagnosis of lung cancer in never smokers is done at later stages than in ever-smokers due to a lower pretest probability of having lung cancer for a never-smoker where the clinician has a different diagnostic suspicion.

Declarations of interest

None

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