Lung Cancer 72 (2011) 9–15

Contents lists available at ScienceDirect

Lung Cancer

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

Review

Lung cancer in never smokers: Change of a mindset in the molecular era

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ARTICLE INFO

Article history:
Received 30 June 2010
Received in revised form 8 December 2010
Accepted 18 December 2010

Keywords:
Non-small cell lung cancer
Never smokers
EGFR
Mutation
Tyrosine kinase inhibitor
EML4–ALK

ABSTRACT

Lung cancer is a leading cause of cancer-related mortality across the world. Although the majority of lung cancer is attributed to tobacco smoke, approximately 25% of lung cancers worldwide occur in lifelong never smokers. Over the past decades, the bulk of research on this disease suggested that several genetic, environmental, hormonal, and viral factors might increase the risk of lung cancer among never smokers. However, there has been no dominant risk factor whose significance has been validated across racial and ethnic groups. However, this subset of lung cancers has received renewed attention due to the introduction of the epidermal growth factor receptor-tyrosine kinase (EGFR-TK) inhibitors showing the dramatic therapeutic response on selected patients with activating *EGFR* mutations which occur more commonly in never smokers. The treatment strategy blocking EGFR pathway in *EGFR*-mutant lung cancer represents a remarkable example of molecular targeted therapies which completely repress tumor by inhibition of driving oncogenes. More recently, a surprising positive effect of an ALK inhibitor on *EML4–ALK*-positive lung cancer has been suggested that lung cancer in never smokers is likely to be an assemblage of molecularly defined subsets which would be a good candidate for personalized diagnostic and therapeutic approaches.

1. Introduction

Lung cancer is a leading cause of cancer-related mortality, with 1.38 million deaths worldwide annually [1]. The majority of lung cancer has been known to be attributed to tobacco smoke. However, approximately 25% of worldwide lung cancers occur in lifelong never smokers [1]. Especially, never smokers have been estimated to constitute about 30–40% of all lung cancer patients in Asian countries [2]. Moreover, several epidemiological studies reported that the proportion of lung cancer in never smokers has been increasing in the general population, although more reliable data to longitudinally assess their time trends are required [3–7]. The mortality rates from lung cancer among male and female never smokers are 17.1 and 14.7 per 100,000 person years, respectively [8]. If it is regarded as a separate category, lung cancer in never smokers would rank seventh as the most common cause of cancer-related mortality, followed by cancers of the cervix, pancreas, and prostate [9].

Over the past decades, a series of researches proposed many genetic, environmental, hormonal, and viral factors as the risk factor of lung cancer among never smokers. Several candidate gene association studies identified two genetic polymorphisms, i.e., Ile462Val of *CYP1A1* and Arg399Gln of *XRCC1*, increased the risk of lung cancer among never smokers [10,11]. Moreover, 5p15.33 (TERT–CLPTM1L), 6p21.33, and 15q25.1 (CHRNA5–CHRNA3) were suggested as the principal candidate genes and genomic loci related with lung cancer risk in never-smokers through genome-wide association studies [12,13]. On the other hand, a vast majority of epidemiological studies have highlighted an association between environmental risk factors and lung cancer in never smokers. The environmental risk factors included environmental tobacco smoke [14,15], radon [16], asbestos [17], and indoor air pollution, such as cooking-oil fumes [18] and coal burning [19]. A high prevalence of human papillomavirus (HPV) 16/18 has been reported among female never-smoking lung cancer patients in China [20]. However, among all possible risk factors, there has been no dominant risk factor whose significance has been validated across racial and ethnic groups. Only one causal risk factor cannot explain the major part of the lung cancer in never smokers. This suggests the complex gene–environment interactions implicated in carcinogenesis of lung cancer.

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doi:10.1016/j.lungcan.2010.12.013

On the other hands, more recent studies about this disease group have focused on its unique biology and its targeted treatment strategy since the development of new antitumor agents, the epidermal growth factor receptor-tyrosine kinase (EGFR-TK) inhibitors, which produce a dramatic therapeutic response on selected patients with activating *EGFR* mutations which occur more commonly in never smokers [21,22]. The treatment strategy blocking EGFR pathway in *EGFR*-mutant lung cancer represents a remarkable example of molecular targeted therapies which completely repress tumor by inhibition of driving oncogenes. More recently, genotype-related sensitivity has also been proven in another group of lung cancer in never smoker, i.e., *EML4–ALK*-positive lung cancer [23]. These results suggest that lung cancer in never smokers is likely to be an assemblage of molecularly defined subsets which would be a good candidate for personalized diagnostic and therapeutic approaches. This review will summarize the comprehensive data from recent researches into lung cancer in never smokers in terms of its distinct genetic alterations and molecular targeted therapies.

2. Distinct genetic changes

Lung cancer in never smokers appears to be driven by a single genetic event, rather than widespread genetic and epigenetic changes, which are observed in the lung cancer in smokers. The genetic changes in several genes such as *EGFR, KRAS, P53*, and *ALK*, in never smokers with lung cancer are critically different from those in smokers with lung cancer (Table 1). These molecular differences make lung cancer in never smokers regarded not simply as a lung cancer unrelated to tobacco-smoking history, but as a distinct disease entity having unique tumorigenesis, clinicopathological features, and chemotherapeutic responsiveness [24,25].

2.1. EGFR mutations

Mutations in the *EGFR*-TK domain are the first genetic mutations more frequently found in lung cancer of never smokers. Classical *EGFR* mutations, which account for about 90% of all these mutations, occur preferentially in specific subsets, such as patients with adenocarcinoma histology, never smokers, those with East Asian ethnicity, and female patients [26,27]. In a review by Shigematsu and Gazdar, 45% of never smokers had *EGFR* mutations, whereas only 7% of smokers had *EGFR* mutations [26]. The high frequency of *EGFR* mutations in never smokers is consistent across different ethnic and geographic groups. Furthermore, it has been reported that the frequency of *EGFR* mutations is inversely associated with the amount of exposure to tobacco smoke, for both passive and active smoking [28,29]. These findings suggest that *EGFR*-mutant tumors, which are closely linked to lung cancer in never smokers, occur by alternative mechanism other than the carcinogenic process induced by tobacco products.

EGFR mutations were detected in the normal respiratory epithelium of 43% of patients with *EGFR*-mutant lung adenocarcinoma [30]. *EGFR* mutations were also detected in early lesions such as atypical adenomatous hyperplasia [31]. Based on these results, *EGFR* mutations seem to develop at an earlier period during the entire pathogenesis of lung adenocarcinoma. Additionally, the finding that *EGFR* mutations are more frequent in the normal epithelium within the tumor (43%) than at adjacent sites (24%) suggests a localized field effect phenomenon [30].

Lung cancers harboring *EGFR* mutations cause a high sensitivity to EGFR-TK inhibitors because these tumors are dependent on the EGFR signaling pathway for their survival and proliferation [32–34]. Interestingly, some genetic variants of driver oncogenes in lung cancer among never smokers, including *EGFR, HER2*, and *EML4–ALK*, show a mutually exclusive pattern, suggesting that an impairment of one pathway common to these genes is critical for this tumor formation and maintenance [35,36].

2.2. KRAS mutations

KRAS mutations are oncogenic missense mutations that develop predominantly in non-small-cell lung cancer (NSCLC) with adenocarcinoma histology [37,38]. *KRAS* mutations are commonly G → T transversions and occur more frequently in smokers with lung adenocarcinoma [39,40]. The frequency of *KRAS* mutations was higher in smokers than in never smokers in the study of 106 patients with lung adenocarcinomas (43% *vs.* 0%; $P = 0.001$) [37]. However, a more recent study done with 482 lung adenocarcinomas by Riely et al. demonstrated that *KRAS* mutations occur in about 15% of the adenocarcinomas of never smokers and that these *KRAS* mutations in never smokers are more likely to be transition mutations, in contrast to those in smokers, which are commonly transversion mutations [41]. On the other hand, *KRAS* mutations are rarely seen in lung cancers with *EGFR* mutations and display a primary resistance to EGFR-TK inhibitors [37].

2.3. P53 mutations

Approximately 40–60% of NSCLCs have mutations in the tumor suppressor gene *P53*, regardless of their *EGFR* or *KRAS* mutation status [42]. These mutations are less common in the lung cancers of never smokers than in tobacco-associated lung cancers [43,44]. Moreover, the types and spectra of *P53* mutations differ significantly according to the smoking status of the patient [39,44–46]. The frequency of G → T transversions is higher in smokers, whereas that of G → A transitions is higher in never smokers [39,44–46]. In the study by Toyooka et al., the G → T:G → A ratio was 1.5 in women smokers and 0.23 in women never smokers [46]. Moreover, mutations at codons 157, 158, 245, and 248 ("warm spots") of *P53* gene were less frequent in never smokers [44].

2.4. EML4–ALK fusion gene

The *EML4–ALK* fusion gene, which is formed by inversions within the short arm of chromosome 2, is a newly identified genetic variant in NSCLC [47]. This was the first oncogenic rearrangement found in lung cancer. The fusion of the N-terminal portion of the *EML4* gene with the intracellular signaling portion of the *ALK* receptor tyrosine kinase gene results in a gain of oncogenic function in the encoded protein [47]. In an unselected NSCLC population, the frequency of the *ALK* fusion gene ranged from 3% to 5% [48]. This fusion gene is more commonly found in adenocarcinomas with an acinar histology, in never or light smokers (<10 pack years), and in young patients, regardless of ethnicity [49–51]. *EGFR* and *KRAS* mutations are mutually exclusive in lung cancers with the *EML4–ALK* fusion [36,50,51].

2.5. Gene expression profiles

Several microarray-based gene expression profiles of patients with NSCLC have reported that hierarchical cluster analysis clearly recapitulates the histological classification of NSCLC, i.e., adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [52–54]. The microarray expression profiles were very different between never smokers and smokers, but there was no clear separation according to smoking status in the hierarchical clustering, either in the nonmalignant tissue or adenocarcinoma [55,56]. This finding may be attributable to the study limitations, such as small sample sizes, so a further large-scaled study is required to confirm the conclusions.

Table 1
Genetic and epigenetic features of lung cancer in never smokers and ever smokers.

Molecular characteristic	Never smokers	Ever smokers	Clinical significance	Reference
Genetic mutations				
EGFR tyrosine kinase mutation	45%	7%	Sensitivity to EGFR-TKI	Shigematsu et al. [37]
KRAS codon 12, 13 mutations[a]				
Total	15%	22%	Resistance to EGFR-TKI	Riely et al. [41]
G → T or G → C transversions	1%	18%		
G → A transitions	14%	14%		
P53 mutations				
G → T transversions	15%	30%	Unknown	Toyooka et al. [46,59]
G → T:G → A ratio[b]	0.23	1.5		
EML4–ALK fusion gene	8.5%	0.8%	Sensitivity to ALK inhibitors	Wong et al. [50]
Epigenetic alterations				
Methylation index[a]	Low	High	Unknown	Toyooka et al. [46,59]
CDKN2A and *APC* methylation[a]	Low	High	Unknown	Toyooka et al. [46,59]
MGMT methylation[a]	66%	47%	Unknown	Pulling et al. [61]

Abbreviation: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.
[a] In the analysis limited to adenocarcinoma.
[b] In the analysis limited to female.

2.6. CpG methylation

Several tumor suppressor genes are inactivated by epigenetic silencing in NSCLC, including CDKN2A, DAPK1, RASSF1A, RAR, APC, CDH13, MGMT, MLH1, MSH2, and GSTP1 [57,58]. The promotor methylation patterns of these genes, which can be associated with significant loss of protein expression, can differ according to the patient's smoking status. The frequency of CDKN2A and APC promoter methylation was lower in patients who had never smoked than in smokers [59,60]. Conversely, the rate of MGMT promoter methylation was higher in the lung cancers of never smokers than in those of smokers [61,62].

3. Molecular targeted therapies

During a decade, targeting the EGFR pathway has been the mainstream of treatment for advanced NSCLC in never smokers. The first-generation reversible EGFR-TK inhibitors, gefitinib and erlotinib, has been established as the first-line treatment of *EGFR*-mutant patients who constitute over 40% of lung cancer in never smokers. Many therapeutic strategies are currently underway to improve the efficacy of the first-generation EGFR-TK inhibitors. More recently, another subgroup harboring a genetic variant which is strongly sensitive to ALK inhibitor has been identified in lung cancer among never smokers.

3.1. EGFR-TK inhibitors

3.1.1. First-generation EGFR-TK inhibitors

The BR.21 trial first demonstrated a survival advantage for erlotinib compared with supportive care in pretreated advanced NSCLC patients [erlotinib to placebo, hazards ratio (HR) = 0.70; 95% confidential interval (CI) = 0.58–0.85] [63]. Another EGFR-TK inhibitor, gefitinib, showed no clinical benefit in previously treated patients with metastatic NSCLC in a randomized phase III study (ISEL) (gefitinib to placebo, HR = 0.89; 95% CI = 0.77–1.02) [64]. However, the ISEL study found that gefitinib was more efficacious than the placebo in the never-smoker group (gefitinib to placebo, HR = 0.67; 95% CI = 0.49–0.92) [64]. The INTEREST study compared gefitinib with docetaxel in advanced NSCLC patients pretreated with platinum-based chemotherapy [65]. The study established non-inferiority of gefitinib compared with docetaxel in terms of overall survival (OS) (gefitinib to docetaxel, HR = 1.020; 95% CI = 0.905–1.150) [65].

A series of clinical trials reported the superior efficacy of EGFR-TK inhibitors in the treatment of never smoker group. Based on these results, a randomized phase III study (IPASS) tested the role of EGFR-TK inhibitors as a first-line treatment for never smokers or light smokers with adenocarcinoma histology in pan-Asia [66]. The IPASS study demonstrated that patients in the gefitinib arm had a better response rate, toxicity profile and progression-free survival (PFS), which was the primary end point, than in the carboplatin–paclitaxel arm (gefitinib to chemotherapy, HR = 0.74; 95% CI = 0.65–0.85) [66]. Especially a planned subgroup analysis reported that the clinical benefit of gefitinib was limited to patients harboring *EGFR* mutations. Nevertheless, the latest final survival data showed that there was no significant difference in OS regardless of *EGFR* mutation status, which might have been a significant cross-over in the chemotherapy arm (gefitinib to chemotherapy, HR = 0.901; 95% CI = 0.793–1.023) [67]. These results from the landmark study were consistent with those from one Korean study (First-SIGNAL) with the same design as the IPASS and two genotype-driven Japanese studies [68–70]. Additionally, a study evaluating the efficacy of first-line erlotinib (EURTAC) is now ongoing in European countries (ClinicalTrials.gov Identifier: NCT00446225). Consequently, these clinical studies allowed EGFR-TK inhibitors to be available as a first-line treatment to *EGFR*-mutant patients.

Several clinical studies evaluated an addition of chemotherapy to EGFR-TK inhibitors [71–75]. The TRIBUTE trial showed that erlotinib with carboplatin and paclitaxel had no a survival advantage over carboplatin and paclitaxel alone in patients with previously untreated advanced NSCLC (erlotinib plus chemotherapy to chemotherapy alone, HR = 0.99; 95% CI = 0.86–1.16) [71]. Moreover, in EGFR FISH-positive group, a response rate was lower for the combination arm [76]. Thus, it has been proposed that there is an antagonistic effect between EGFR-TK inhibitors and chemotherapy when they are given concomitantly [77]. The study just suggested a possible advantage for maintenance erlotinib after the completion of chemotherapy in EGFR FISH-positive patients [76].

3.1.2. Acquired resistance mechanisms

Patients who have a marked response to EGFR-TK inhibitors finally experience progression of the disease. Complicated and variable mechanisms contribute to the resistance to EGFR-TK inhibitors. First, secondary point mutations on the *EGFR* gene, such as T790M, D761Y, T854A, and L747S have been discovered in patients showing acquired resistance [78–82]. Secondary T790M mutation in exon 20, which leads to the sterical hindrance of gefitinib or erlotinib binding, is the most common mechanism of acquired resistance, arising in about 50% of these cases [78]. Second,

Table 2
New tyrosine kinase inhibitors in clinical development to overcome resistance to first-generation EGFR-TKI in advanced NSCLC.

Class	Drug	Target	Phase	Design
EGFR-targeted therapeutics				
EGFR/HER2 inhibitor	BIBW2992 (Afatinib)	EGFR, HER2	Phase III	*vs.* erlotinib and *vs.* getinib
	HKI-272 (Neratinib)	EGFR, HER2	Phase II	Alone
	BMS-599626	EGFR, HER2	Phase I	Alone
	AV-412/MP-412	EGFR, HER2	Phase I	Alone
Pan-HER inhibitor	PF-00299804	EGFR, HER2/4	Phase II	Alone or *vs.* erlotinib
	EKB-569 (Pelitinib)	EGFR, HER2/4	Phase II	Alone
EGFR/VEGF inhibitor	ZD-6474 (Vandetanib)	EGFR, VEGFR2, RET, FLT1	Phase III	*vs.* placebo or *vs.* erlotinib
	XL647	EGFR, HER2, VEGFR2, EPHB4	Phase II	Alone
	BMS-690514	EGFR, HER2/4, VEGFR1/2/3	Phase II	*vs.* erlotinib
	AEE788	EGFR, HER2, VEGFR2	Phase I	Alone
Non-EGFR targeted therapeutics				
MET	ARQ197	MET	Phase II	Plus erlotinib *vs.* erlotinib alone
	PF-02341066 (Crizotinib)	MET, ALK	Phase I/II	Plus erlotinib *vs.* erlotinib alone
	GSK1363089 (Foretinib)	MET, VEGFR,	Phase I/II	Plus erlotinib *vs.* erlotinib alone
	XL184	MET, VEGFR2, RET	Phase I/II	Plus erlotinib *vs.* erlotinib alone
HSP90	IPI-504 (Retaspimycin)	Hsp90	Phase I/II	Alone
	17-AAG (Tanespimycin)	Hsp90	Phase I	Alone
PI3K/AKT/mTOR	Temsirolimus	mTOR	Phase I	Plus erlotinib
	Everolimus	FKBP-12, mTOR	Phase I/II	Plus erlotinib or gefitinib
	Ridaforolimus	mTOR	Phase II	Alone
	MK2206	AKT	Phase I	Plus gefitinib
	XL147	PI3K	Phase I	Plus erlotinib
VEGFR	Sorafenib	VEGFR2/3, Raf, PDGFR-β, c-Kit	Phase II	Alone or plus erlotinib
	Sunitinib	VEGFR1/2/3, FLT, PDGFR-β, c-Kit	Phase III	Plus erlotinib *vs.* erlotinib alone
	OSI-930	VEGFR2, c-Kit	Phase I	Plus erlotinib

Abbreviation: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

it was reported that the ERBB3 signaling pathway is reactivated by *MET* gene amplification, which causes about 20% of TK inhibitor-resistant tumor [83]. However, in half of *MET* amplification cases, secondary T790M mutation is coexistent [84]. In addition, recent preclinical studies have suggested the reduced expression or loss of PTEN, a negative regulator of PI3KCA [85], HGF-mediated MET activation [86], and a loss of IGF binding proteins with subsequent activation of IGF-1R [87], as the acquired resistance mechanism. Based on these potential molecular mechanisms, various therapeutic trials have been underway to prevent or treat tumors resistant to EGFR-TK inhibitors (Table 2).

3.1.3. Second-generation EGFR-TK inhibitors

Several irreversible TK inhibitors that covalently bind to the kinase domain of EGFR, including XL647, BIBW2992, HKI272, PF299804, and BMS690514, represent second-generation EGFR-TK inhibitors. These EGFR-TK inhibitors showed the promising efficacy on overcoming the resistance acquired with the T790M mutation in preclinical model. Currently, the main treatment strategy for drugs in this class is to treat selected patients with *EGFR* mutations before or after the development of resistance to the first-generation EGFR-TK inhibitors.

In the studies of BIBW2992, which irreversibly inhibits EGFR and HER-2, the LUX-Lung 2 phase II study tested this drug as a first- or second-line treatment for 129 patients with advanced NSCLC harboring activating *EGFR* mutations. This drug showed a response rate of 60%, a disease-control rate of 86%, median PFS of 14 months, and median OS of 24 months for the overall group [88]. However, diarrhea and skin disorders were the most frequently observed adverse events and main causes of dose reduction. The leading pivotal phase III trial, called LUX-Lung 1, is investigating BIBW2992 *vs.* placebo in NSCLC patients who were previously treated with erlotinib or gefitinib [89]. Although BIBW2992 did not meet the primary endpoint of extending life compared to placebo (BIBW2992 to placebo, HR = 1.08; 95% CI = 0.86–1.35), this drug significantly extended PFS compared to placebo with some improvement in cancer-related symptoms (BIBW2992 to placebo, HR = 0.38; 95% CI = 0.31–0.48) [89]. On the other hand, a pan-EGFR blocker, PF299804 showed significantly longer PFS than erlotinib in a randomized phase II trial in pretreated advanced NSCLC patients (PF299804–erlotinib, HR = 0.67; 95% CI = 0.48–0.94) [90].

3.1.4. c-MET inhibitors

Several clinical trials testing MET inhibitors (XL184, MetMab, and ARQ197) plus EGFR-TK inhibitors are ongoing in EGFR-TK inhibitor-naïve or -treated NSCLC patients [91,92]. ARQ-197 is a selective, non-ATP competitive inhibitor of c-MET receptor tyrosine kinase. In a phase II clinical trial of erlotinib plus ARQ 197 *vs.* erlotinib plus placebo as a second/third-line treatment in EGFR-TK inhibitors-naive NSCLC patients, ARQ-197 was well-tolerated and prolonged PFS (erlotinib plus ARQ 197 to erlotinib plus placebo, HR = 0.81; 95% CI = 0.57–1.15). The benefit in PFS is particularly observed among patients with non-squamous histology, *KRAS* mutations, and EGFR wild-type status. In the study with MetMab which is an anti-Met monoclonal antibody, the addition of MetMAb to erlotinib in patients with Met positivity in immunohistochemistry improved both PFS and OS with no unexpected safety profile, whereas Met negative patients had worse PFS and OS with MetMAb, and more severe grade toxicity [93].

3.2. ALK inhibitors

An ALK inhibitor is a new, targeted drug for lung cancers that carry the *EML4–ALK* fusion gene. Crizotinib (PF 02341066) is an oral, small-molecule tyrosine kinase inhibitor with activity against the MET/HGF and ALK. In a recent phase I trial, an ALK inhibitor demonstrated promising efficacy in *EML4–ALK*-positive patients [23]. Of the 82 evaluable patients, 47 (57%) had an objective response and another 27 (33%) experienced disease stabilization. The adverse event of grade 3 or 4 was an increase in liver enzymes (12%). This ALK inhibitor is now under investigation in a phase III trial in *EML4–ALK*-positive patients, in a comparison with pemetrexed or docetaxel as second line therapy.

4. Conclusions

Currently, lung cancer in never smokers constitutes a significant portion of all lung cancers worldwide. Lung cancer in never smokers is considered to be a distinct disease from those in smokers in the view of the pathogenesis, molecular alterations, drug responsiveness and prognosis. Recent studies have discovered a significant portion of lung cancer in never smokers harbor a genetic variant in a driving oncogene, to which molecular targeted drugs are dramatically sensitive. These observations have led to changes in the overall treatment strategies for lung cancer. Therefore, a genetic testing before the treatment is considered essential for lung cancer in never smokers in order to select the appropriate treatment option according to the patient's molecular characteristics.

Conflict of interest statement

Dr. Cho reports receiving lecture fees from Roche and Astrazeneca, and consulting fees from Bristol-Myers Squibb and GlaxoSmithKline; Dr. Mitsudomi receiving honoraria from AstraZeneca, Chugai, Daiichi-Sankyo, Pfizer, and Taiho and attending the advisory board meeting of Pfizer, Boeringer-Ingelheim, AstraZeneca, Kyowa-Kirin, Bayer, and Chugai; and Dr. Mok receiving consulting fees from Roche, Astra-Zeneca, Pfizer, and Eli Lilly, lecture fees from Roche, AstraZeneca, and Eli Lilly, and a research grant to the Chinese Lung Cancer Research Foundation from AstraZeneca, Hong Kong. No other potential conflict of interest relevant to this article was reported.

Acknowledgements

This study was supported in part by a faculty research grant of Yonsei University College of Medicine for 6-2010-0061, and by a grant of the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A101956).

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