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Review Article

Tobacco control and lung cancer

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Abstract

Tobacco smoking is a major risk factor for early death, and smoking cessation is an important public health issue as it has health benefits. Passive smoking is a significant health concern for children and non-smoking adults. Lung cancer is the world's leading cause of cancer-related mortality, and tobacco exposure is responsible for the majority of cases of the disease. However, the incidence of lung cancer in patients that have never smoked is increasing. Smoking prevention measures aim to reduce the overall number of smokers and the age-adjusted frequency of lung cancer. The use of equipment designed to prevent smoking, including e-cigarettes and devices against passive smoking, is warranted to protect children.

Introduction

Tobacco smoking is a major risk factor for early death and disease and has killed more than 5 million people worldwide every year since 1990 [1]. In Japan, the speculated number of deaths ascribable to smoking in 2005 was 196,000, which represented 18% of all deaths. The leading cause of smoking-ascribable deaths was malignant neoplasms [2]. Lung cancer is the world's leading cause of cancer-related mortality, and tobacco exposure is responsible for the majority of cases of the disease, but the incidence of lung cancer among people that have never smoked is increasing [3]. In this article, we will discuss recent tobacco control topics related to oncology, with particular focus on lung cancer.

Tobacco control and smoking cessation

Many types of cancer and respiratory or cardiovascular disease are associated to smoking, which brings more medical matters than alcohol, drugs, and high cholesterol levels. Smoking cessation is an important public health issue, as it has intermediate and long-term health benefits. Thus, smoking cessation measures that were widely available, accessible, and cost-effective would have great public health benefits. In addition, passive smoking is an important health issue for young and non-smoking adults and develops to cause bronchial asthma, meningitis, sudden infant death syndrome, and inflammation of the middle ear [4]. Thus, smoking prevention remains as a matter of most important matters and needs aggregative policy and personal procedure [5], it is high priority that exact data on the health effects about smoking sufficiently valuable to statespersons and the general public. A large global study (the Global Burden of Disease 2015 Tobacco collaborators' study) was recently reported [6]. It found that of all global deaths 6.4 million (11.5%) were attributable to smoking. Furthermore, it was demonstrated that the number of smokers worldwide had decreased to 933.1 million (males: 768.1 million, females: 165 million), 52.2% of which were living in one of four countries (China, India, the USA, and Russia). The top 10 countries in terms of the sizes of their smoking populations are shown in (Figure 1). The age-standardized worldwide prevalence of daily smoking was 25.0% for males and 5.4% for females in 2015, which represented 28.4% and 34.4% reductions, respectively, on the numbers seen in 1990 [6]. In Japan, the prevalence of smoking was 29.7% for males and 9.7% for females in 2016, which represented 52.6% and 6.0% reductions, respectively, since 1965 (Figure 2) [7].

Frequency of smoking and the lung cancer mortality rate

"How can the reduction in the frequency of smoking and the concomitant increase in the lung cancer mortality rate be explained? The reason is that there is no relationship between tobacco smoking and lung cancer". This is the view of the pro-smoking lobby. Is it true? Certainly, the frequency of male smokers is decreasing, as shown in (Figure 2), and the lung cancer mortality rate is increasing (from 11.201 per 100,000 people in 1965 to 87.194 per 100,000 people in 2015), as shown in Figure 3. However, the frequency of cancer generally increases in old age. In developed countries around the world, such as Japan, populations are becoming markedly older, and the number of patients with lung cancer has consequently increased. Therefore, age-adjusted cancer-related mortality per 100,000 people is used for epidemiological comparisons of the numbers of cancer patients. The age-adjusted lung cancer mortality rates for each sex in Japan are shown in (Figure 3) [8]. The frequency of lung cancer peaked in 1996, and the subsequent reduction was considered to have been due to a drop in the number of tobacco smokers. As people who smoke tobacco will not develop cancer for many years after they start smoking, the lung cancer mortality rate is expected to peak about 30 years after the frequency of smoking peaks.

Passive smoking

Passive inhalation of smoke pouring from cigarette has various harmful actions to children. The children of tobacco smokers are attacked by nicotine and other baleful chemicals both in the uterus

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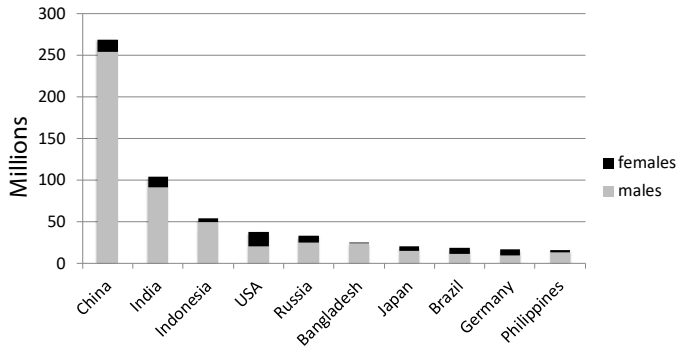

Figure 1. Top 10 countries ranked according to the sizes of their smoking populations.

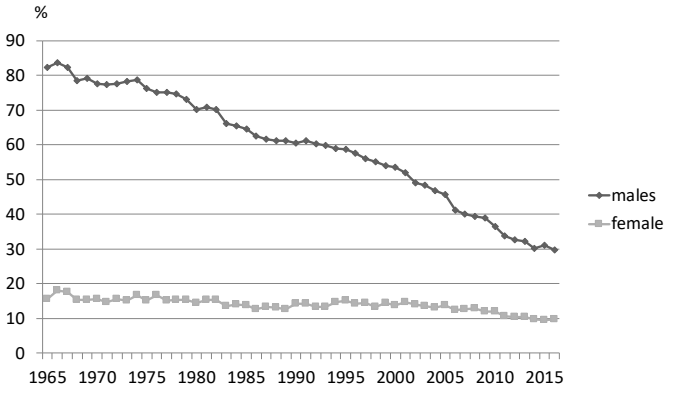

Figure 2. Adult tobacco habit (%) transition in Japan.

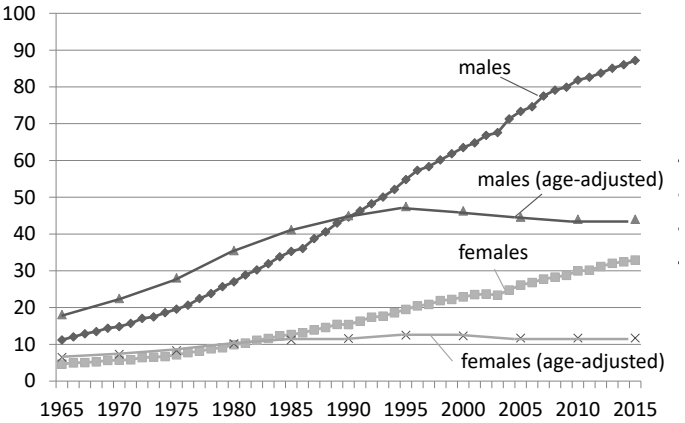

Figure 3. Mortality rate and age-adjusted mortality rate of patients with lung cancer per 100,000 people in Japan.

and in their home environments. Exposure during intrauterine life to smoke pouring from cigarette brings poor birth offspring and affects lung, brain, and cardiovascular growth, which places such children at enlarged risk of harmful consequences later in life, disorders like adiposeness, actionable disturbance, and cardiovascular-related disorders [9]. In addition, most smokers initiate smoking in early adulthood, when they are at increased risk of becoming addicted to nicotine. It is warranted that development of biomarkers which express tobacco chemical influence to health in childhood and rest of life.

To produce a pooled estimate of the relative risk of lung cancer associated with exposure to passive smoking in women who have never smoked, but whose spouses smoke, Taylor *et al.* conducted a meta-analysis of 55 studies, including cohort, population-based case-control, and non-population-based case-control studies [10]. The pooled relative risk of lung cancer for these women was found to be 1.27 (95% confidence interval [CI]: 1.17-1.37), and a causal relationship between passive smoking and lung cancer was demonstrated to exist. A systematic review by Hori *et al.* clarified the relative risk of lung cancer in secondhand smokers in Japan. The latter review identified nine epidemiological studies encompassing 12 populations, and the pooled relative risk of lung cancer associated with secondhand smoke exposure was estimated to be 1.28 (95% CI: 1.10-1.48) [11]. Recent meta-analyses of secondhand smoke exposure and lung cancer are listed in Table 1 [10-13]. Almost all of these meta-analyses reported an overall relative risk of lung cancer of 1.2-1.3 [10], whereas the overall relative risk of small cell lung cancer was 3.09 [13]. In the Liberal Democratic Party, the governing party of Japan, there is now debate about whether to strengthen legal measures to curb secondhand smoke in public places before the 2020 Tokyo Olympic and Paralympic Games.

E-cigarettes

Electronic cigarettes (e-cigarettes) are aggressively merchandised in tune with Internet, TV, magazines, sport contents, and advertising displays, etc. E-cigarettes are generally promoted as a harmless replacement to traditional cigarettes and/or as a quitting smoking adjuvant [14, 15]. Although e-cigarettes appear to cause less harm as a nicotine delivery device than conventional cigarettes, they seem to be a gateway to traditional cigarette smoking in adolescents. E-cigarettes described easier to stop using, a cut down or the complete quitting of traditional cigarette smoking and an improved subjective health status and smokers who used e-cigarettes would encourage e-cigarettes to other smokers [16]. The British Medical Association [17], Public Health England [18], and the American Association of Public Health Physicians [19] consider that e-cigarettes have a role to play in reducing the harm of tobacco smoking. By contrast, The World Health Organization [20], World Lung Foundation [21], and World Medical Association give a caution to using of e-cigarette.

Very few controlled studies have investigated the acute toxicities associated with e-cigarettes. Exposure to the primary component of the e-liquid, propylene glycol, is generally considered safe, but this chemical can irritate the upper and lower respiratory tract. When heated, it produces formaldehyde and acetaldehyde, which are both toxic [22]. Several case reports have described suicide attempts involving the liquid found in e-cigarettes. Two of these individuals had very high levels of nicotine in their venous circulation after they intravenously injected or ingested the liquid [23, 24], and two other cases involved individuals who had ingested nicotine in much higher quantities than the immediately dangerous to life or health concentration (IDLH) level, but did not die [25, 26]. E-cigarettes can cause increases in blood pressure and heart rate and have the potential to cause cardiac events and arrhythmias in people who have or are at risk of cardiac disease [27]. Most of the suggested cardiac effects of

Table 1. Recent meta-analyses of secondhand smoke exposure and lung cancer.

Author	Year	Studies	Relationship	Relative risk
Taylor[16]	2007	12	Yes	1.3
Kim[18]	2014	18	Yes	1.31*
Jayes[17]	2016	13	Yes	1.41
Hori[15]	2016	9	Yes	1.28

The estimated association with secondhand smoke exposure was greater for small cell lung cancer than for non-small cell lung cancer (odds ratio=2.11).
*1.26 for adenocarcinoma, 1.41 for squamous cell carcinoma, 1.48 for large cell lung cancer, 3.09 for small cell lung cancer

e-cigarettes are secondary effects of the nicotine, rather than being caused by the other components of the e-liquid [28]. Carnevale *et al.* conducted a crossover, single-blind study of the effects of e-cigarettes vs. conventional cigarettes on oxidative stress and endothelial function in healthy smokers and non-smoking adults [29]. Although e-cigarettes seemed to have less impact, oxidative stress increased, and nitric oxide levels and vasodilation decreased after e-cigarette use. Vardavas *et al.* studied whether using an e-cigarette for 5 minutes has an impact on pulmonary function or the fraction of exhaled nitric oxide in healthy adult smokers [30]. As a result, a reduction in the nitric oxide level and acute increases in respiratory flow resistance and overall peripheral airway resistance were detected. These two studies demonstrated that e-cigarettes rapidly alter vascular function; i.e., they reduce nitric oxide synthesis and small airway function while increasing airway resistance. Lanza *et al.* studied the frequencies of e-cigarette and conventional cigarette use in US middle and high school students aged 11-19 (n=22,007) [31]. The frequency of e-cigarette use increased faster than the frequency of conventional cigarette use from the ages of 13-16. E-cigarette use was strongly associated with conventional cigarette use, particularly during early adolescence [odds ratio: >40 before age 12]. The recent increase in e-cigarette availability has resulted in many individuals using these devices without knowing about the possible adverse consequences. Healthcare providers should educate e-cigarette users, especially children, about the risks associated with accidental exposure to the liquid found within them.

The increase in the number of lung cancer patients that have never smoked

Measures aimed at reducing the frequency of smoking have decreased smoking prevalence rates for both males and females and lung cancer mortality rates in many countries [32]. Although tobacco smoking is a major risk factor for lung cancer, it is estimated that 25% of lung cancer cases involve patients that have never smoked, and it is the seventh most common cause of cancer-related mortality [33]. Lung cancer in people that have never smoked is now regarded as a distinct disease entity that is separate from smoking-related lung cancer, as there are differences in the histological characteristics, age at diagnosis, stage at presentation, and survival outcomes of the two forms of the disease [34-36], and actionable driver oncogene mutations are more frequent in cases of non-small cell lung cancer (NSCLC) involving patients that have never smoked [37-39]. Two of the most common actionable driver mutations associated with lung cancer in patients that have never smoked are an activating mutation in the kinase domain of the epidermal growth factor receptor gene (EGFR) and chromosomal rearrangement involving the anaplastic lymphoma kinase gene (ALK) [40-43]. The etiologies of these actionable driver mutations in lung cancer patients (regardless of smoking status) remain unknown. Estrogen has been reported to transactivate growth factor signaling pathways, including the EGFR axis, and these effects appear to be reciprocal [44, 45]. In addition, the effects of passive tobacco smoking and the aging of society remain potential etiologies of lung cancer in individuals that have never smoked. The absolute number [the number of affected individuals per 100,000] of lung cancer patients who have never smoked is actually increasing. We do not know the exact reason why the frequency of lung cancer is increasing among patients that have never smoked and so this issue needs further study.

Low-tar filter cigarette smoke

Cellulose acetate filters brought more porous cigarette papers and decreased 37mg to 22mg for the tar of a cigarette during 1950 and 1960s [46]. Moreover, the development of air infiltration bores in the filter tip resulted low tar (commonly 8-14 mg) and very low tar (equal to or less than 7 mg) cigarettes in the late 1960s. At the same time, the mean tar volume per cigarette reduced to 13 mg in US by 1990 [46]. Close directional movement in standardized tar blew up to the UK [47, 48] and other countries. In Japan, shifting from nonfilter to filter cigarettes observed around 1965 [49, 50]. Indeed, the WHO Framework Convention on Tobacco Control (FCTC) has recommended the removal of tar and nicotine numbers from packages [51]. Low-tar filters mostly cart off the bigger particles in cigarette smoke that have tendency to be caught in the middle thick bronchus which is the area squamous cell carcinoma occur. By contrast, low-tar filters do not cart off smaller particles that have tendency to arrive the peripheral of the lung which is the area adenocarcinomas occur. It is hypothesized that the temper adenocarcinoma increase compare with squamous cell carcinoma in various countries due to the spread of low-tar filter cigarettes. In addition, low-tar filter smokers have tendency to inspire deeply compare with those of nonfilter cigarettes, resulting in cigarette smoke arriving the peripheral area. This hypothesis is supported by the several studies. It is documented that the risk of lung adenocarcinoma is many times higher for current smokers than non-smokers, *i.e.*, 19.0-fold for men and 8.1-fold for women in the Cancer Prevention Study (CPS) II (1982-1984) from US, while in CPS I (1959-1961) corresponding estimates were 4.6-fold for men and 1.5-fold for women [52]. European countries also documented that the risk of lung adenocarcinoma was much higher for current smokers than non-smokers, *i.e.*, 8.0 times higher for men and 4.1 times for women in a case-control study conducted in 6 countries (1988-1994) [53], while in a case-control study in 5 countries conducted previously (1976-1980) corresponding estimates were 3.5 and 1.8 for men and women, respectively [54].

Tobacco smoking and lung cancer histologic type

Lung cancer come into existence by smoking, however, there is an attitude it for single disease but capture and research independent disorder separated by histological types. Kreyberg *et al.* [55] divided lung cancer into two groups based on the result of case study separated by histological types of patients with lung cancer which compare the tobacco smoking rates, and advocate group I tumors (squamous, large, and small cell carcinoma) which related tobacco smoking tightly and group II tumors (adenocarcinoma) which have uncertain etiological relationship with tobacco smoking. Analytical epidemiology researches which confirm Kreyberg hyposis include the reports of Doll et al [56] and Shimizu et al [57]. Doll *et al.* [56] conducted hospital based case control study that research relationship with 872 male patients with lung cancer (832 cases in Kreyberg group I and 40 cases in group II) and tobacco smoking. The result, dose-response relationship was observed between daily tobacco smoked number and lung cancer risk in Kreyberg group I, however, in Kreyberg group II it was small sample size and not observed obvious relationship to tobacco smoking. Although Doll also studied with female patients with lung cancer and observed tendency of dose-response relationship, the conclusion was sustained because group II was small sample size (13 cases). Shimizu et al [57] selected the patients visited Aichi Cancer Center Hospital Respiratory Department who diagnosed lung cancer afterward and control cases and conducted case control study by matched pair analysis. The result, relative risk of smokers was high as 7.0 in Kreyberg group I (63 pairs) and confirmed dose-response relationship, however, confirmed only slightly higher rate of 1.3 (or 1.5 for current smokers) in group II (36 pairs).

By contrast, Stayner *et al.* [58] and Weiss et al [59] reported relationship between adenocarcinoma which included in Kreyberg group II and tobacco smoking in a proactive manner. Stayner et al [58] conducted case control study and research relationship with tobacco smoking about between male patients with lung cancer (152 squamous cell, 50 adenocarcinoma, and 45 small cell carcinoma) which selected 9 areas of The Third National Cancer Survey (TNCS) and population-based control. In the result, age-adjusted relative risk of smokers was all significantly higher as 5.1, 3.1, and 3.1 in small cell carcinoma, squamous cell carcinoma, and adenocarcinoma, respectively. Although the dose-response relationships were observed all histological types, it was not statistical significant in adenocarcinoma. Weiss *et al.* [59] identified smoking status of 6,136 male participant ≥ 45 years old at the beginning of a study of Philadelphia Pulmonary Neoplasm Research Project (PNRP), and follow up over 10 years, and calculated lung cancer affect risk by person-year method. In the results, dose-response relationship between number of tobacco smoked and lung cancer affect risk was observed in not only well-differentiated squamous cell cancer (23 cases) and small cell carcinoma (8 cases) but also adenocarcinoma (14 cases), and was not observed in poorly differentiated squamous cell carcinoma (13 cases) and large cell carcinoma (4 cases). Lubin *et al.* reported the relationship of smoking and lung cancer histology as part of large scale hospital base case control study in Europe (7,804 cases and 15,207 control cases). It was strongly suggested the positive significant dose-response correlation between lung cancer risk and duration of smoking, amount of smoking and degree of inhale, and negative significant dose-response correlation between length of smoking cessation not only in squamous cell carcinoma (3,708 males, 272 females) and small cell carcinoma (1,172 males, 199 females) alone, but in adenocarcinoma (716 males, 223 females) in both male and female, and strongly suggested causal association between smoking. Sobue et al conducted a population-based cohort study of 91,738 men and women, and 422 lung cancer incident cases were analyzed during 1990-1999 [60]. The relative risk for all incident cases associated with current smokers versus non-smokers was 4.5 and 4.2 for men and women, respectively. When separated by histologic type, relative risk for small cell carcinoma and squamous cell carcinoma were 17.5 and 12.7, while for adenocarcinoma it was 2.8 and 2.0 for men and women, respectively. This result suggested that current cigarette smoking is related with an increased lung cancer risk about 10- to 20-fold for small and squamous cell carcinoma and 2- to 3-fold for adenocarcinoma.

Tobacco smoking and immune checkpoint inhibitors

Immunotherapy has become as a new treatment choice for patients with advanced NSCLC. Several comparative clinical trials clearly articulated that immune checkpoint inhibitors leaded superior survival outcomes compared to chemotherapy in patients with advanced NSCLC [61-66]. Some studies with immune checkpoint inhibitors in NSCLC suggested that smoking history was associated with improved survival outcomes. Kim *et al.* conducted meta-analysis to investigate if survival benefits of immune checkpoint inhibitors in patients with advanced NSCLC are different according to smoking status and 2,389 ever-smokers and 413 never-smokers were included from 6 studies [67]. In first-line treatment setting, immune checkpoint inhibitors tended to improve PFS in patients with smoking history (HR = 0.85, P=0.07), however, chemotherapy was significantly associated with improvement of PFS (HR = 2.30, P=0.009) for never-smokers. In more than second-line setting, immune checkpoint inhibitors significantly prolonged OS over that with chemotherapy in ever-smokers (HR= 0.70, P<0.00001), however, immune checkpoint inhibitors failed to significantly improved OS for never-smokers with NSCLC (HR=0.79, P=0.12). Nishio M, *et al.* recently reported phase II study of nivolumab for patients with advanced or recurrent non-squamous non-small cell lung cancer and current/former smokers were more responsive to treatment than non-smoker (ORR 29.1% vs 4.8%) [68]. Smoking status may will be a predictive marker for survival to immune check point inhibitors.

Conclusion

In conclusion, smoking prevention measures aim to reduce the overall number of people who smoke and the age-adjusted frequency of lung cancer. The use of equipment designed to prevent smoking, including e-cigarettes and devices against passive smoking, is warranted in order to protect children.

Conflict of interest

The authors report that no potential conflicts of interest exist.

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