Occupational and environmental carcinogens in epidemiology of lung cancer in South Indian population

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Abstract

The present epidemiological study assessed smoking and non-smoking lung cancer patients with pesticide and other environmental exposures as additional risk factors. 152 confirmed lung cancer patients were screened and all patients were divided into four different groups based on epidemiological findings, we found increase in lung cancer incidences in the category where smoking habit with exposure to pesticides was highest ((p =0.0006) followed by smoking habit and environmental carcinogens as risk factor. The incidence of lung cancer increased with age where probability was $p<0.025$ in the age group of 50-70 years. Pesticides and other carcinogenic exposures are added burdens in smokers as tobacco smoke contains several carcinogenic compounds and heavy metal contaminants such as cadmium, which are harmful to the lungs. This is the first report of our findings which recommends the inclusion of pesticide exposure in relation to/or in combination with smoking habits in epidemiological data. Since tobacco smoke contains heavy metals like cadmium - a known carcinogen and prolonged exposure to pesticides increases cancer incidence in smokers and these are modifiable risk factors in lung cancer that can be counseled.

Keywords: Lung cancer; Smokers; Carcinogens; Pesticides; Epidemiology; Tobacco; Cadmium.

Introduction

The most common cause of lung cancer is long-term exposure to tobacco smoke since tobacco smoke contains carcinogens and heavy metals. Lung cancer was initially thought to be infrequent in India (Parkin et al., 2000). Tobacco consumption either as tobacco chewing or smoking and the use of cigarettes was the leading cause of avoidable mortality accounting for 50% of all cancers in men. According to some reports, the epidemiological data showed rising prevalence of the disease in Indian population and smoking reported as the causative agent for 85% of bronchogenic carcinoma cases. During the 1950s, the evidence was clearly sufficient to establish the carcinogenicity of tobacco smoking (Doll, 1998). By the end of the 1950s, convincing evidence linking smoking with lung cancer and other cancers was obtained from case–control and cohort studies. Carcinogens, both organic and inorganic like heavy metals were identified in

tobacco smoke. Cigarette smoke condensate was shown to cause tumors when painted on the skin of mice. Sirsat (1958) reported that lung cancer formed one percent of all cancers in Tata Cancer Hospital. Viswanathan et al (1982) collected information from different hospitals of the country (India) and reported that the incidence of lung cancer in hospital population was 27.4 per million in the 1950's which increased to 78.6 per million in 1959 subsequently steadily increased each year. Previous reports on smoking document the fact that smoking was an important contributory factor in the causation of lung cancer (Hammond and Horn, 1958). Banker (1955) also reported an increase in the incidence of bronchogenic carcinoma (16.1 in 1950 to 26.9 in 1961 per 1000 malignancies), following analysis of the records of 15 teaching institutions in India over a period of 10 years. Nearly 5 million people die due to tobacco use every year and this figure will increase to 10 million by the end of 2020.The smoker to non-smoker ratio was 2.7:1. However, some studies

found the smoker to non-smoker ratio was 20:1. Small cell type carcinomas were predominated in patients up to 40 years of age and had a weaker association with smoking. After the age of 40 years, squamous cell type was common in smokers and adenocarcinoma in non-smokers (Jindal et al., 1982; Jindal et al., 1987; Jussawala and Jain, 1979; Narang et al., 1970 and Pakhale et al., 1985). Further reports from the above authors document that around 80% of lung cancer patients came from the rural areas. In patients with lung cancer, a history of active tobacco smoking was present in at least 87% of males. History of passive tobacco exposure was reported in only three percent of cases. Along with smoking, certain occupations carry a higher risk of lung cancer (Coultas and Samet, 1992). Different types of occupational exposures and exposure to pesticides play a crucial role in the development of various cancers. However, the exact mechanism and its correlation to confounding factors were not identified. Few toxicological studies on exposure to various pesticides and their genotoxicity were proven but these studies also did not relate to cancer cases. Smoking cessation and prevention efforts have been successful, although currently about one in four adults still smoke cigarettes.

Farmers mostly ended up with lung cancer, may be because they rely heavily on the use of chemical pesticides to get rid of their pest problems. Farmers use 85 percent of the 2.6 million metric tons of active ingredient of pesticides produced annually in crop production in developing countries. The modern farming methods totally depend on synthetic fertilizers and an array of pesticides exposing the farmers to the harmful chemicals in the environment. World Health Organization (1992) reports that roughly three million pesticide poisonings occur annually and result in 220,000 deaths worldwide. Both economically and in terms of human life, these poisonings represent an enormous cost for society. Approximately 80% of the pesticides produced annually in the world are used in developed countries (WRI/UNEP/UNDP,1994). Less than half of all pesticide-induced deaths occur in these countries and some of them end as cancer deaths (Jocket, 1992). A higher proportion of pesticide poisonings and deaths occur in developing countries where there are inadequate occupational safety standards, and insufficient enforcement; poor labeling of

pesticides; illiteracy; and insufficient knowledge of pesticide hazards (Jocket, 1992). Throughout the world, the highest levels of pesticide exposures are found in farm workers, pesticide applicators, and people who live adjacent to heavily treated agricultural farms. Because farmers and farm workers directly handle 70-80% of the pesticides, they are at greater risks due to pesticide exposure (Pimentel and Greiner, 1997). Different types of occupational exposures to pesticides play a crucial role in the development of various cancers. The epidemiological evidence suggests a significantly higher rate of cancer incidence among farmers and farm workers in the US and Europe than among non-farm workers (McDuffie, 1994). There is a possible association between pesticide exposure and infertility, besides cancers of testis, breast, prostate, ovaries (Cantor et al., 1992), also hematopoietic, and nervous system cancers (Koifman and Meyer, 2002). In these high-risk populations, there is strong evidence for associations between lymphomas, soft-tissue sarcomas, and certain herbicides (Fleming et al., 2003) as well as between lung cancer due to exposure to organochlorine insecticides (Zahm et al., 1980).Such data are heterogenous and not recorded in any epidemiology studies.

The limited epidemiological evidence regarding a number of organochlorine insecticides and several cancers generally supports the toxicological evidence of an association with cancer. Among the male farm workers of over 50 years, the use of chlorinated pesticides (OC) and methyl bromide were significantly associated with prostate cancer, which is the second most common cancer in men, after lung cancer (Pesatori et al., 1994). The International Association for Research on Cancer (IARC) evaluated OC insecticides (DDT, chlordane, heptachlor, toxaphene), as being either possibly carcinogenic to humans or not classifiable as carcinogenic (aldrin, dieldrin, lindane). Systematic information on occupational risk for lung cancer patients is rarely available in India. Four studies examined the association between lung cancer and pesticide exposure (Zahm et al., 1980; Kross et al., 1992; Figa-Talamanca et al., 1993 and Alavanja et al., 2003). Results of these studies are somewhat difficult to interpret as only two studies collected information regarding smoking status and such studies are not well documented in lung cancers in the Indian

population even though the medical fraternity is fully aware of such dangers.

Therefore, the aim of this study was to identify the additional risk factors in lung cancer, which could form an important part of epidemiological data. It will be useful to correlating these findings with environmental exposure to carcinogens. India is a country of farmers, where they widely use pesticides in fields for crop protection, and smoking is their joy and pleasure hence these parameters play an important role in determining the importance of additional risk factors in lung cancers more so because, the potential to detect lung cancer early and save lives is being revisited.

Patients and methods

This study had the prior approval of the ethics committee responsible for studies on humans. Informed patient consent was obtained prior to data collection on demographics.

Study group
The study subjects consisted of all cases of lung cancer cases confirmed either by cytological or histological evaluation, and staging assessed and classified as per TNM guidelines by Pathologists. Patients from various parts of Andhra Pradesh from different cancer hospitals, from 2009 to 2010, formed our study group. All subjects verbally agreed individually to participate in the study. Having assured the confidentiality of all information about the subjects the patients were interviewed in the presence of their close relatives. Details recorded in a structured questionnaire at the time of the interview. Information about their education, occupation, family history of cancer, present and past medical history, diet pattern, smoking habit, history of alcohol intake, present and past heating and cooking system at home, exposure to any environmental pesticides/carcinogens, were obtained. Details of past and present occupational history recorded for all subjects. All the subjects were categorized in two groups; I and II. These categories further divided into two sub categories A and B. Category IA consists of patients who were smokers with exposure to pesticides and Category IB consisted of those who were

smokers with exposures to other carcinogens like asbestos and non–specific environmental exposures. Category IIA consisted of those who were non-smokers with exposures to pesticides and Category IIB consisted of non-smokers with exposures to other carcinogens like asbestos and nonspecific environmental exposures. The fifth group was all other cases of lung cancer that did not fall into these four categories.

Recording of demographic factors
Questionnaire included socio-economic characteristics and other variables such as age, sex, education level, income level, marital status average size of a family, average age at marriage etc, occupation - included information like location of different work places, duration worked in those occupations, types of industries and job duties. Based on the occupational history, subjects were divided into exposed and non-exposed groups concerning carcinogenic agents. Exposure prone occupations like agriculture, construction of buildings, construction of roads and bridges, manufacturing, and transport were categorized as exposed occupations. Similarly, occupations like administrative services, business, student and housewives categorized as non- exposed.

Statistical analysis
Data analyzed by mean, standard deviation (SD) and percentages for age, sex ratio, and histological cancer cases. In addition, wherever required data were subjected to chi-square analysis, RR values and CI 95% to derive the significance of correlation in statistical terms and significance of the study data submitted as P-value using OpenEpi Version 2 software.

Results
The present study included 152 patients,about 114 (74.50%) were males and 38 (24.8%) were female subjects. Median age for all subjects was 57 years (range 20-90 years), while median age for males was 59.4 years, and females was 50.2 years. The age distribution of these patients is presented in Table 1 along with other demographic factors. Incidence of cancer risk was found to increase with age where chi-square was 17.33 and probability was $p<0.025$.

Table 1: Age and sex of the subjects in relation to prevalence of lung cancer.

Age Group	Males	Percentage	Females	Percentage	No. of Patients & Percentage	Chi square	P value
Less than 40	4	33.33%	8	66.66%	12 (7.84)		
41- 50	21	65.62%	11	34.37%	32 (20.9)		
51 -60	40	78.43%	11	21.56%	51 (33.33)	17.33	0.0016*
61-70	37	84.09%	07	15.09%	44 (28.75)		
71 and above	13	92.85%	1	7.14%	14 (9.15)		
Total	115		38				

Demographic data of smokers, non-smokers and sex ratio in pesticide and other carcinogenic exposure group is presented graphically in figures. The histological types are presented in figure 1 and figure 2. The most common histopathological type was Squamous cell carcinoma (SCC) (68 cases 44.73%), followed by adenocarcinoma (AC) (46 cases 30.26%), others (30 cases 19.73%) and Small cell lung cancer (SCLC) (08 cases 5.26%). The histology pattern was found to be non-significant with mean age (table 2).

Table 2: Diagnosis of subjects at presentation.

S. No.	Histology Type	Males	Females	Total (%)	Mean Age in years	Agricultural workers M	Agricultural workers F	Others M	Others F
1	Adenocarcinoma	35	11	46 (30.26)		17	05	18	06
	Smokers	15	00	15	58.04	12	00	03	00
	Non-smokers	20	11	31		05	05	15	06
2	Squamous Cell Carcinoma	51	17	68 (44.73)		32	05	19	12
	Smokers	37	00	37	57.91	28	00	09	00
	Non-smokers	14	17	31		04	05	10	12
3	Small Cell Lung Cancer	07	01	08 (5.26)		05	00	02	00
	Smokers	04	00	04	60	03	00	00	00
	Non-smokers	03	01	04		02	00	01	01
4	Other* Smokers Non-smokers	21	09	30 (9.73)		14	02	07	07
		15	00	15	54.5	10	00	05	00
		06	09	15		04	02	02	07

*Not otherwise specified lung cancer histology type
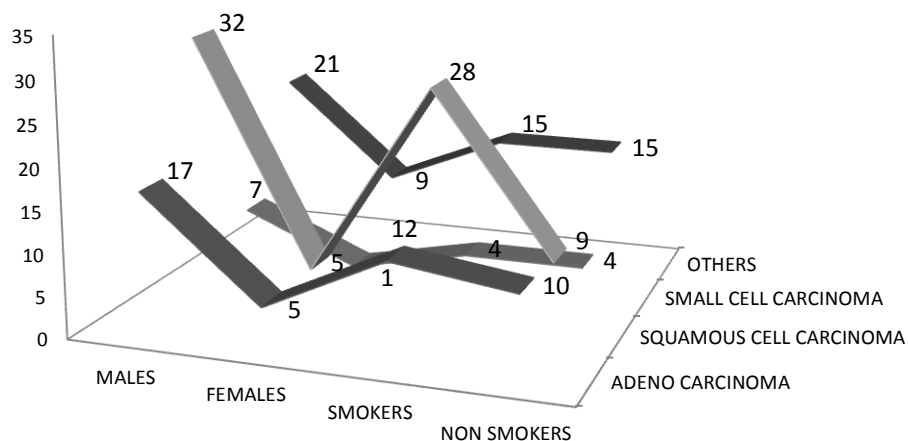
Figure 1: Graphical representation of smokers, non-smokers and sex ratio in pesticide exposure group.
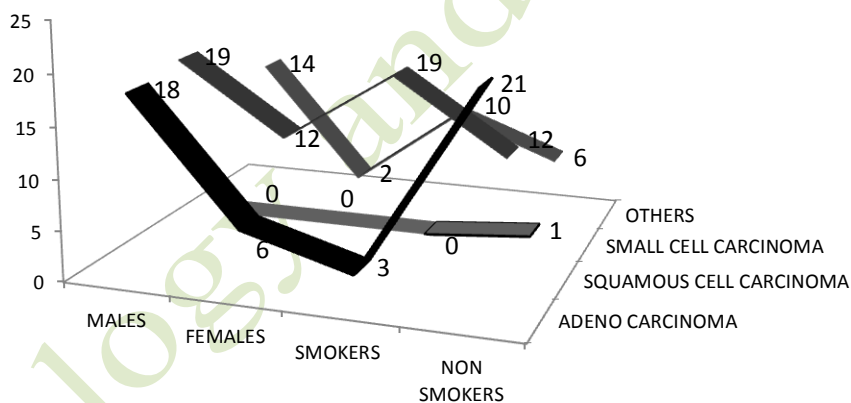

Figure 2: Graphical representation of smokers, non-smokers and sex ratio in other carcinogen exposure group.

Table 3 summarizes the statistical analysis of smokers versus non-smokers in all the four categories of lung cancer cases with pesticide exposure and other exposure group. As seen in Figure-3, smoking with exposure to pesticides had a higher risk factor as compared to smoking without pesticide exposure whereas nonsmoking history with pesticide exposure or other carcinogen exposures had lower risks (figure- 4). In adenocarcinoma the probability was 0.0116 vs 0.5150 and risk rate was 1.92 as compare with 0.525 (table-3). In squamous cell carcinoma (SCC), the probability was 0.0006 vs 0.011 and risk rate was 2.21 as compared with 2.084. In the other histological group the probability was 0.0009 vs 0.210 and risk rate was 2.14 as compared to 1.42 9 (shown

in Table-3). In the case of small cell lung carcinoma (SCLC), no significant finding was observed as probability was 0.715 vs 0.400 and risk rate was 1.18 as compared to 1.5. Overall risk in smokers with pesticide exposure showed a significant risk factor as compared with nonsmoker group with pesticide exposure

group in SCC 85.33% followed by SCLC 82.35%, Adenocarcinoma 75.56% and other group 68.85%. In the other group, patients having smoking habits also showed a significant risk factor for lung cancer, as the overall risk was 84.85% followed by adeno 70.18%, SCC 60.32% and SCLC was 33.33%.

Table 3: Risk factor analysis of smokers and non-smokers with respect to pesticide exposure.

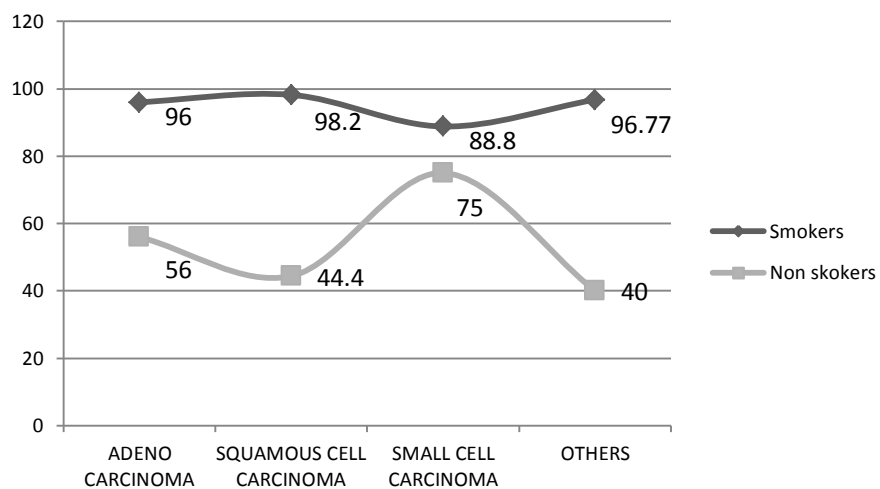| Histology | Smoking status | Occupational Exposure | | | | | | | | | | | |
		Pesticides						Others					
		M	F	RR	95% CI	P-value	Risk (%)	M	F	RR	95% CI	P-value	Risk (%)
Adenocarcinoma	Smokers	12 5	0 5	1.92	1.023-3.60	0.0116	96 50	03 15	00 06	0.525	0.03-9.0	**0.5150**	37.5 71.43
	Non Smokers												
Squamous Cell Carcinoma	Smokers	28 4	0 5	2.21	1.06- 4.59	0.0006	98.2 44.4	09 10	0 12	2.084	1.2-3.3	0.011	94.74 45.45
	Non Smokers												
Small Cell Lung Cancer	Smokers	4 3	0 1	1.18	0.6 - 2.2	**0.715**	88.8 75	0 0	0 1	**1.5**	0.07-29.9	**0.400**	50 33.33
	Non Smokers												
Other	Smokers	15 6	0 9	2.41	1.29- 4.52	0.0009	96.77 40	10 4	0 2	1.42	0.7-2.5	**0.210**	95.24 66.67
	Non Smokers												

Figure 3: Risk analysis of pesticide exposure in smokers and non-smokers.
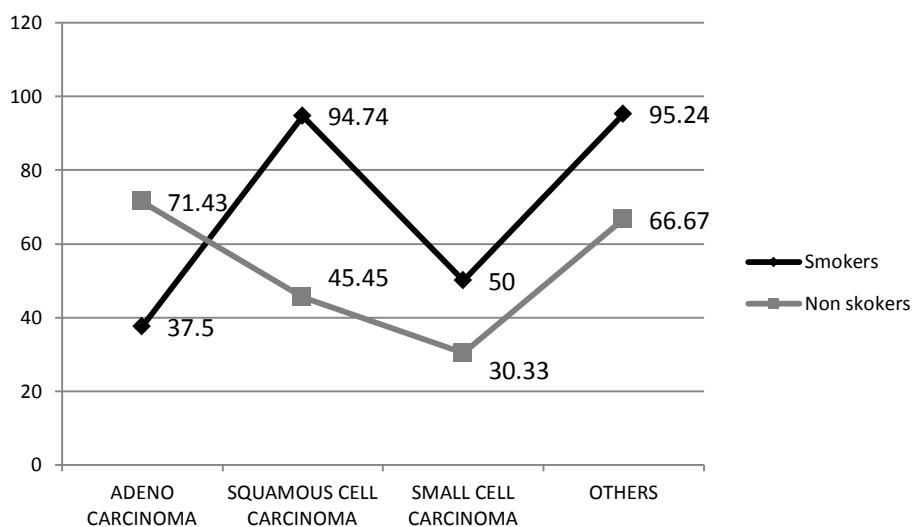

Figure 4: Risk analysis of other carcinogen exposures in smokers and non-smokers.

Discussion

This study focused primarily on human epidemiological evidence linking smoking with pesticide exposure and lung cancer in south Indian population. In this study, 71 cases were male smokers and, 81 cases were non-smokers. Nevertheless, the risk was equal in smokers and non-smokers due to pesticide and other carcinogen exposures. Bolognesi (2003) reported that pesticides were specifically

responsible for carcinogenesis and this has been documented in many human studies. We found an association between smoking with pesticide exposure and report a higher risk as compared with smoking without pesticide exposure. Several previous studies also showed smoking cigarettes was a strong risk factor for lung diseases in the Agricultural Health Study. The relation between pesticide exposure and lung cancer was not proven but was only indicated.

The present study showed evidence that those who were smokers and had exposure to pesticides had significant risk of lung cancer as compared with non-smokers with exposure to pesticides, similarly those who were smokers or non-smokers exposure to other factors also showed lower risk as compared with smoking with pesticide exposure. The mechanisms by which pesticides contribute to cancer causation vary, and a pesticide may act in more than one way to manifest its effects. Among the major mechanisms, genotoxic effects were shown to produce direct changes in DNA (Bolognesi, 2003; Palus et al. 2003, and Yang et al., 2003), and as reported in *in-vitro* studies by us earlier (Jamil et al., 2004; Jamil et al., 2005; Rambabu and Jamil, 2005). Few reports suggest that heavy metals like cadmium and its compounds, arsenic and mercury, are common food and water contaminants, and are well document as causative agents in various types of bronchial and lung diseases and various cancers. The IARC has classified cadmium as a human carcinogen on the basis of sufficient evidence in both humans and experimental animals (Aldridge et al., 2003). IARC, however, noted that the assessment was based on few studies of lung cancer in occupationally exposed populations like agricultural workers, smelters etc. Pesticides and tobacco products contain some of the heavy metals, specifically cadmium and its compounds; we find evidence of its relevance in lung cancers. Cigarettes contain cadmium (1,300+ng) and therefore the risk of lung cancer and other malignancies seems to be significantly increased by environmental exposure to the metal cadmium. Biological monitoring of cadmium in the general population has shown that cigarette smoking may cause significant increases in blood cadmium (B-Cd) levels, the concentrations in smokers being on average 4–5 times higher than those in non-smokers. As the half life of cadmium is 10 to 30 years, it

accumulates in the human body, particularly in the kidneys (Jarup et al., 1998), Cadmium carbonate and cadmium chloride have been used as fungicides and both exposures may lead to increased lung cancer incidence in smokers.

Some studies on various populations exposed to arsenic, such as pesticide manufacturers, smelter workers, and miners, who are smokers consistently demonstrate an excess in lung cancer cases (Staessen in 1999). Because cigarettes contains arsenic (500+ ng) reports show a strong relation between arsenic exposure in carcinogenesis process, as reported by Staessen (1999) he further showed that there was an association between cadmium and arsenic exposure, because these two components are major ingredients in cigarettes and pesticides. Although all these groups were exposed to other chemicals in addition to those mentioned by us, there is no other common factor that could explain these findings. Some authors suggested that the susceptibility to pesticides depends mostly on the gene polymorphism at certain chromosomes on which the cancer genes are present. Thus, different individuals show varying degrees of response, while others believe that chronic exposures are critical (Nawrot et al., 2006; Persson et al., 1993 and Sabitha et al., 2010). We found that the risk was equal in smokers with or without history of exposure to carcinogens, except in SCC group as all groups showed probability < 0.002. The same situation occurred with home and environmental exposures where multiple exposures products were used, and their doses unmeasured, and their names long forgotten by those exposed. Smoking is the main risk factor along with other carcinogenic exposures prevalent in smoke-filled environments.

Pesticide exposure was the leading cause of all types of lung cancers among non-smokers. Factors contributing to these population differences may include both underlying genetic susceptibility as well as exposure to carcinogens including coal smoke, aerosolized cooking oils, and second hand smoke. Studies evaluating gene-environment interactions may provide important insights into carcinogenesis pathways of lung cancer in never smokers. Approximately 10 to 15% of all lung cancers arise in never smokers, making lung cancer in never smokers one of the leading causes of cancer-related mortality

(Jindal et al., 1995; CDC, 2005). Few reviews have suggested a possible link between pesticide exposure and certain cancers (Thun et al., 2006). Other researchers have recommended further investigations due to limitations in the innate design of cohort and case-control studies (Jamil et al., 2007 and Maroni, 1993). The studies varied in terms of number and types of subjects, types of pesticides studied, ways of measuring exposure, covariates examined, and follow-up periods.

Scrutiny of our study revealed that men with lung cancer had been exposed to pesticides in addition to smoking habits, which was a significant risk group. It also explains the seeming sex difference, because exposure to smoking and pesticides and other exposures is far more common in "male jobs". The exposed men had mostly been occupational agricultural workers. We suggest that epidemiological and demographic studies should include an assessment of pesticide exposures as well as heavy metal exposures, in the blood and urine samples of subjects. The present study typically relies on indirect measures of exposure, such as type of occupation and specific pesticides, which are not named nor quantified. Covariates, such as family history, smoking duration, and race, are not always available. Since we evaluated smoking with pesticide exposure with a prior hypotheses linking with human lung cancer risk, we cannot rule out the possible association with pesticides that might induce lung cancer risk. In our study, many of our patients came from agricultural background and since their occupation in agriculture involves use of multiple chemical agents (including pesticide and fertilizer chemicals), it is often difficult to determine what agent is directly linked to a specific end-point. Nevertheless, we are still challenged to develop public health strategies for preventive measures, to reduce deaths and suffering of those destined to develop lung cancer.

Acknowledgement

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