Smoking, Air Pollution and Cancer: Global Epidemiology, Public Health and Genomics

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Abstract
This paper discusses the epidemiology and public health of smoking, air pollution and cancer. This paper goes into some details of quantitative methods used to analyze the relationship between smoking, air pollution, cancer, and the associated human costs. These quantitative aspects are important to precisely understand the impact of smoking and air pollution on public health. Smoking and air pollution have huge human cost both in suffering and in monetary terms. Healthy clean air is a global resource. International effort in controlling smoking and air pollution is fundamental in improving global public health.

Introduction

Smoking and air pollution are two known risk factors of cancer [1]. Relationship between tobacco smoking and lung cancer was first established in 1950 [2]. Aerosols are air born particles or droplets measured about 1 micrometer, heavier particles would settle down [3]. When wood or other organic matters are burnt, it produces a complex mixture of gases and small particles [4]. Fine particles with a aerodynamic (assumed spherical for generally irregular particles) diameter less than 2.5 micrometers are called PM2.5 and those less than 10 micrometers are called PM10, and particles with diameter between 2.5 micrometers and 10 micrometers are called course particles [4]. PM10 particles are small respiratory particles and could penetrate deep into alveolar level, and PM2.5 particles mostly settle in the alveoli, and even smaller particles less than 100 nanometers could goes through the alveoli and into internal organs [5]. Gaseous and particulate air pollution is a major cause of mortality and morbidity worldwide [6-11]. Coarse particle air pollution is less harmful than the fine particle air pollution [6-12].

This paper discusses the epidemiology and public health of smoking, air pollution and cancer [7,12-14]. This paper is a part of a series of papers discussing modern challenges facing oncology in general and radiation oncology in particular [15-23]. This paper does not intend to be exhaustive, but make choices on challenging and important areas related to public health of smoking and air pollution. This paper goes into some details of quantitative methods used to analyze the relationship between smoking, air pollution, cancer and the associated human costs. These quantitative aspects are important to precisely understand the impact of smoking and air pollution on public health.

Smoking, adverse health effects and cancer

For an excellent textbooks on statistics used in epidemiology see [24] and modern epidemiology see [1]. In one study the odds ratio (OR) of lung cancer and history of chronic disease was 12.7 for smokers and 2.6 for non-smokers [25]. Chronic Obstructive Pulmonary Disease (COPD), was previously known as chronic bronchitis and emphysema, is defined as post-bronchodilator FEV1 (forced expiratory volume in 1 second) to FVC (forced vital capacity) ratio < 0.70 [26]. The OR was 3.2 for COPD and 83.7 for tuberculosis [25]. In 2005, about 673000 deaths were attributable to tobacco smoking, the leading cause of deaths from smoking included 268200 from cancer, 146200 from cardiovascular diseases and 66800 from respiratory diseases [27].

In this study cardiopulmonary effects of smoking [28], participants were recruited form a Boston community on the ground floor of an apartment building. The information of medication, cardiac and pulmonary symptoms, and smoking history were collected [28]. Continuous Holter monitoring, respiratory rates and blood pressure were measured through cycles of rest, standing, exercise (walking a small incline), recovery by lying down and slow breathing [28]. The slow breathing part allowed evaluation of pollution on heart rate variability (HRV) [29,30] independent of respiratory rate [28]. During exercise, the sympathetic tone takes over from the vagal tone which dominates the rest periods, the heart rate increases and HVR decreases [28]. Heart rate was lowest during slow breathing [28]. The standard deviation of RR intervals (SDNN) and the squared root of the mean of the squared difference between normal RR intervals[31] (r-MSSD) [28]. 163 Holter monitoring sessions were recorded for 21 participants [28]. The median body mass index was 25.6 kg/m² (range 18.5 to 33.3 kg/m²), the median age was 73.3 (range of 53 to 87 years) [28]. This study found that the effect of smoking was mediated through decreased ability of cardiovascular response to stress as measured by decreased HRV [28].

Protecting children from second hand smoke

Second hand smoking causes 5000 deaths in children, three times more than all childhood cancers combined and other important health consequences [32,33]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32]. In one study, the tobacco smoke exposure (TSE) was measured by measuring the continue level [32]. Dried blood spots collected from a national sample of 1541 Black and White children was analyzed for lead and continue levels [32]. Continue was detected in 61% of dried blood spots, 17% had continue and White children was analyzed for lead and continues levels [32]. Significantly higher level higher than 3 monograms per gram [32].
and inhibits myocardium’s ability to use oxygen to create adenosine triphosphate, increases platelet activity, accelerates atherosclerosis, and increases tissue damage after ischemia or myocardial infarction [34]. Second smoking from parental smoking is a preventable cause of morbidity and mortality in children, it causes direct medical expenditures of $4.6 billion, and loss of life cost of $8.2 billion in 1993 dollars [33].

In 2008, 54% of children aged 3 to 11 years old had exposure to TSE as measured by continue in urine or blood based on a study using National Health and Nutrition Examination Survey (NHANES) data [35]. Passive smoking can cause heart disease and lung cancer in nonsmoking adults, and the risk of sudden infant death syndrome, acute respiratory infections, middle-ear disease, and exacerbation of asthma in children [35]. Exposure to second hand smoke decreased about 70% from late 1980s to 2002 because of widespread implementation of smoking ban in indoor workplaces and public places [35]. In one study, 135 parents of nonsmoking children with cancer who lived with smokers were selected, approximately 43% of families prohibited smoking at home, and there were about 71% and 52% lower continues levels from homes with no or partial smoking restriction [36].

Air pollution, adverse health effects and cancer

In 1997, the Environmental Protection Agency (EPA) imposed new ambient PM2.5 standard that was challenged by industrial groups but eventually upheld by the U.S. Supreme Court [37]. China did not include PM2.5 in their air quality assessment that had led to a discrepancy between person feeling about the air quality and the government announced pollution index [38]. China uses “blue sky” as a surrogate of measured PM10 less than 150 microgram/m3, which is 2.5 times higher than the WHO (World Health Organization) guideline [39]. PM2.5 level will be included in 113 cities in 2013 and all cities in China by 2015 [39]. China has daily average limits for PM2.5 at 75 microgram/m3, and PM10 at 150 microgram/m3; in Japan the daily average limits for PM2.5 is 35 microgram/m3, and PM10 at 100 microgram/m3 [5].

Wuhan is a city of more than 9 million in central China [40]. In one study, the mean PM10 level was about 150 microgram/m3 at urban areas and about 200 micrograms at industrial sites [40], this was 3-4 times higher than U.S. and E.U. standards [40]. Mineral toxins (e.g. Pb and As (mainly from car batteries [41,42], and Cd [43]) were very high [40]. These were mainly from uncontrolled waste products from cement and steel manufacturers, coal fired power plants [40].

In a 2013 study using a National English Cohort, the hazard ratio of all cause mortality associated with PM2.5, NO2, and SO2 were estimated to be 1.02, 1.03 and 1.04 respectively; for lung cancer was 1.02, 1.06, and 1.05 respectively [44].

A counterfactual experiment of effects from air pollution

The Beijing Olympic provided a counterfactual (inferred) experiment [1,24,45,46] for the adverse effects of pollution on health since no one would perform an actual controlled experiment of increasing pollution on healthy individuals because of the principle of “do no harm” first. The counter factual causality is an inferred but rigorous causality analysis. This is similar to not being able to, under controlled condition switch the gender of an individual to estimate the causality of gender [1,24,46]. Chinese Government spent 10 billion dollars on cleaning up 13% - 60% of Beijing’s air pollution for 2008 Olympics for a two months period [47]. The resultant level was 4-9 times worse than average air pollution in major U.S. cities during the same time period [39,47]. In one study [45], biomarkers of inflammatory and oxidative responses were measured before, during and after the Beijing Olympic Games (exhaled nitric oxide, H+, nitrite, nitrate and 8-iso-prostane) and urinary 8-hydroxy-2-deoxyguanosine in 125 Beijing medical student participants [45]. A mixed effect model was used to assess the effects of air pollution on these biomarkers [1,24,45]. From pre-Olympic high pollution period to during Olympic low pollution period, there was a decrease of about -4.5% to - 72.5% in all biomarkers [45]. From during Olympic to post-Olympic higher pollution period, there was an increase of about 48% - 360% in all biomarker levels [45]. These studies confirm the important roles of oxidative stress and pulmonary inflammation in the ill effects of air pollution [45]. The effects of the Beijing counter factual air pollution experiment were much higher than previous similar experiments including 1996 Atlanta Olympic because of the higher pollution background in Beijing [47]. Epidemiological studies of health effects are important because legitimate pollution concerns of residents have lead to public policy readjustment in European countries [48].

Carcinogenesis, Genomics and Biomarkers

Currently, human genome could be sequenced very effectively and relatively inexpensively [19,49]. Some of the mutations resulted from environmental mutagens could occur in germ cells and passed on to unexposed offspring [49,50]. International experts are gathering to assess and potentially compile a list of gremlin mutagens [49,50].

As early markers of clinical outcomes, simple and easy to obtain biomarkers from body fluids have been used as surrogate early endpoints of smoking for lung cancer [51] and cardiopulmonary disease [51,52]. In one study, 10 ml of venous blood was drawn for polymerase chain restriction-length polymorphism [53]. The biomarkers tested in this study [53] were 8-oxoguanine DNA glycosylase 1 (hOGG1), apurinic/apyrimidinic end nuclease 1 (APE1), and adenosine deaminase (ADAT) that were important in DNA base excision repair pathway [53]. The biomarkers tested in this study [53] were 8-oxoguanine DNA glycosylase 1 (hOGG1), apurinic/apyrimidinic end nuclease 1 (APE1), and adenosine deaminase (ADAT) that were important in DNA base excision repair pathway [53].

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(UGT) and glutathione-S-transvers (GST) and these enzymes are associated with genetic polymorphism [64]. In one study, data and DNA samples from Tennessee Colorectal Polyp Study were used and showed a relationship between tobacco metabolism genetic polymorphism and risk of colorectal polyps [60].

Somatic mutations in the tyrosine kinases (TK) domain of the EGFR and genes downstream of EGFR signaling (KRAS, BRAF) and PI3K-AKT pathways are related to lung cancers [65]. EGFR activating mutations predominantly occur in adenocarcinoma of never-smoker, East Asian ethnicity, and female lung cancer patients [65]. 30% of lung cancers of East Asians have EGFR mutations [65,66]. 25% of lung cancer patients were never smokers [67,68]. There were more EGFR mutations in never smokers, and recently suppressing effects of ALK inhibitor on EML4-ALK positive lung cancer of non-smokers showed the driver ontogenesis for these patients may be different [67]. In one study, lung cancers in never female smokers attributed to household solid fuel coal use was genetically different from tobacco smoking [66]. There was a high frequency of EGFR Exon 18 and KRAS mutations [66], and low mutation frequency of EGFR exon 21 [66]. This study found among the 15 EGFR mutations, nine were point mutations, four were exon 19 deletions, and one was on Exon 20 insertions [66]. Among the six KRAS point mutations, 5 were found in adenocarcinoma and one in squamous carcinoma [66]. In another study, EGFR and KRAS mutations were analyzed for 124 patients with non-small cell lung cancers [69]. Activating mutations were found in 62.7% of 126 patients and KRAS in 2 of 114 patients [69]. About 75% of the EGFR mutations occurred in female in this study [69]. There was about a 5-fold increase in EGFR mutation rate for each year of continuous exposure to tobacco smoke [69].

The risk of childhood cancer may increase with exposure to environmental pollution (e.g. nitrogen oxides) [11,70-72]. The odds of acute lymphoblastic leukemia (ALL) increased about 10-20% per 25 ppb (10^-9) increase of nitric oxides [11]. Second and third exposure increased the odds of bilateral retinoblastoma in this study [11]. In this study, there were 58 hepatoblastoma cases identified in New York State Cancer Registry from 1985 to 2001, after adjustment of birth weight, there was an increase relative risk of 2.1 for maternal smoking [73]. Methodologically, studies using addresses at diagnosis allows estimation of childhood exposure and studies using birth places would allow estimation of prenatal exposure [11].

Polychlorinated biphenyls (PCBs) [74] are banned in U.S. in late 1970s but are common in household items [75]. The blood level of PCB has not changed and could be as high as 30 times of the ambient/background air level [75,76]. The environmental PCB levels are highest near industrial complexes such as waste facilities, coal power plants, and various types of incinerators [75,77,78]. Carpet PCB dust has associated with non-Hodgkin lymphoma [79].

Eliminating Human Burden of Diseases Caused by Air Pollution

Adverse health effects of air pollution are associated with very large economic costs [80]. In this study, the relative risk (RR) of lung cancer mortality per 10 microgram/m^3 increase was assumed to be 1.14 [12]. RR for lung cancer mortality was used as an approximation of lung cancer incidence [12]. It was assumed that by calculating (1-inverting the RR), it estimated the reduction in incidence per 10 microgram/m^3 decrease of PM2.5 for CHD (coronary heart disease), COPD, stroke, and lung cancer [12]. The cost estimation used a method that took into account censoring [81]. The cost saving was about 0.1 to 2.6 million euro per 100000 inhabitants for the four diseases [12].

In U.S. it was estimated in a 2002 study, every 10 microgram/m^3 increase in PM2.5 was associated with about 4% increase in all cause mortality, 6% in cardiopulmonary mortality and 8% in lung cancer mortality [8]. In this population based study, all white lung cancer patients from Los Angeles and Honolulu from 1992-2008 Surveillance Epidemiology and End Results database [82]. The hazard ratio was 1.48 per 10 microgram/m^3 for PM10 (particles less than 10 micrometers in diameter) [82], and similarly for PM2.5 and ozone [82]. It is estimated 7 million premature deaths are attributable to air pollution [83].

Globally, India is the most polluted country in the world [83]. air pollution was estimated to kill half a million people in China in 2013 [83]. In this study on the entire 4.5 million population of United Arab Emirates (UAE), it estimate the death attributable to outdoor pollution, indoor pollution, drinking water, coastal water, work environment, and climate change [84]. Outdoor pollution was found to be the major cause of death related to these six environmental factors [84]. Ulaanbaatar, Mongolia has a population over 1.3 million and an elevation of 1310 meters [85]. This study used land use regression (LUR) technique and mobile monitoring [14] and estimated mortality attributable to air pollution [14]. This study estimated wintertime spatial patterns of NO2 and SO2 based on 2 weeks of measurements at 37 locations and freely available geographic predictors [14]. The wintertime average concentration of PM2.5 was 148microgram/m^3. The wintertime average PM2.5 concentration measured in a traditional housing was 250 micro/m^3 [14]. Air pollution accounted for about 10% of city’s mortality and 40% of deaths from lung cancer [14].

Because of increase in economic activities and pollution, the cause of deaths in China has changed [86]. In a 2006 study, a nationally representative cohort of 169871 men and women 40 years or older were selected [86]. The five leading causes of death for men were 374.1 per 100000 person-years for cancers, 319.1 for heart diseases, 310.5 for cardiovascular disease, 54.0 for accidents, and 50.4 for infectious diseases [86]. For women, 268.5 for heart diseases, 242.3 for cardiovascular diseases, 214.1 for cancers, 45.9 for pneumonia and influenza, and 35.3 for infectious diseases [86]. The percent of risk that were preventable were 11.7% for hypertension, 7.9% for tobacco smoking, 6.8% for physical inactivity and 5.2% for underweight (BMI below 18.5) [86]. This study suggested an increased control of hypertension, smoking cessation, increased physical activity and improved nutrition should be the most important strategies for preventing premature deaths in China [86].

In this 1999 study, 970000 inhabitants of Rhone-Alpes region in France (Lyon, Grenoble, and Chambery) were probabilistically sampled [87]. The per capita income in 2012 of the region was $39798 [88]. The average particulate air pollution concentrations in these three cities were respectively 39, 41 and 10 microgram/m^3 [87]. The attributable fractions of respiratory symptom air pollution were
between 0.6% and 13.8% [87]. The cost of illness attributable to the air pollution in this study was between 79 million (20th percentile) and 135 million Franc (80th percentile) for one million people (one French Franc is worth about $0.2 currently) [87]. About 40% of the cost was for over the counter medication, and about 40% of the cost was related work loss, and hospital admission accounted for about 5% of the cost [87].

In this 2006 study, it was estimated the public health impact of PM2.5 (mostly inferred from PM10 concentration in this study), in 23 European cities [89], a reduction of PM2.5 exposure to 15 microgram/m³ would extend life expectancy of a 30 years old by one month to more than two years [89]. Air pollution was estimated to cause 6% of mortality in Austria, France and Switzerland [7].

**Saving Lives by Eliminating Socioeconomic Barriers**

Socioeconomic barriers, especially income and education level, are known to adversely affect the outcome of cancer patients [90-103]. American Cancer Society (ACS) each year compiles the cancer incidence, mortality and survival data from the Centers for Disease Control and Prevention (CDC), The North American Association of Central Cancer Registries, National Center for Health Statistics [104]. 1.6 million of new cancer cases, and 0.6 million cancer deaths were projected for 2011 [104]. Eliminating socioeconomic disparities remains a great challenge, and it could avoid 37% (about 60000 cancer deaths) premature deaths in U.S. in 2007 alone [104].

Xuanwei is city of more than 1 million people in Yunnan, China [105]. In this study, 21232 farmers in Xuanwei were followed from 1976 to 1992 [106]. Most residents burned “smoky” coal in fire pits, but since 1970s, most residents changed to stoves with chimneys [106]. The risk ratio for lung cancer decreased to 0.59 for men and 0.54 for women. Indoor air pollution decreased to less than 35% compared to before the improvement [106]. 10 years after the stove improvement, the decrease in lung cancer risk became unequivocal compared to before the improvement [106]. This relatively inexpensive stove improvement prevented many premature deaths from indoor pollution in poor neighborhoods.

**Conclusion**

Smoking and air pollution have huge human cost both in suffering and in monetary terms. Healthy clean air is a global resource, about 20% of ground pollution in U.S. may be attributed to air pollution in Asia [39]. PM2.5 is considered a modifiable causal risk factor in cardiovascular mortality and morbidity [107]. International effort in controlling smoking and air pollution is fundamental in improving global public health.

**Post-logue: Recks not the perils of the heat of mid-day sun**

New York City is a truly pleasant city especially around the New Year [108]. Not to miss a beautiful day, I took a walk down the street to a bookstore near the intersection of 14th Street and Broadway hoping to find a book to read. It was around 3 o’clock, the midday sun was eerie and the ambience was hazy.

Someone said where one walked, sat and gazed were not random. I remembered, during last summertime, Alaska’s midnight sun, the last of summer wine [109].

Shakespeare perhaps wrote his Midsummer Night’s Dream after he visited the north in his youth, and saw the midnight sun [110] changed into moonshine.

As opposed to exact like and dislike, most of the time I found books agreeable or disagreeable.

I brought All the Light We Cannot See.

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