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SERIES "THE GLOBAL BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"
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Epidemiology and costs of chronic obstructive pulmonary disease

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INTRODUCTION: AN INTERNATIONAL WORKSHOP ON THE GLOBAL BURDEN OF COPD

Chronic obstructive pulmonary disease (COPD) is a leading but under-recognised cause of morbidity and mortality worldwide [1]. The prevalence of COPD in the general population is estimated to be ~1% across all ages rising steeply to >10% amongst those aged ⩾40 yrs. The prevalence climbs appreciably higher with age. The 30-yr projections for the global increase in COPD from 1990–2020 are startling. COPD is projected to move from the sixth to the third most common cause of death worldwide, whilst rising from fourth to third in terms of morbidity within the same time-frame [2]. The cofactors responsible for this remarkable increase are the continued use of tobacco, coupled with the changing demographics of the world, such that many more people, especially those in developing countries, are living into the COPD age range.

COPD is under-diagnosed not only in its early stages, but even when lung function is severely impaired. This is perhaps surprising, since simple and inexpensive spirometers that are suitable in clinical practice are now available, and lung function is a powerful predictor of all-cause mortality, regardless of smoking status. No other disease that is responsible for comparable morbidity, mortality and cost is neglected by healthcare providers as much as COPD. It may well be that the true burden of the disease is not fully appreciated, and the message that COPD is both preventable and treatable has yet to be fully understood by most healthcare providers. The hope is that highlighting these facts will help to raise the profile of COPD and begin to change long-held attitudes.

Up to 2001, only 32 prevalence surveys of COPD had been reported [3]. This is remarkable given the hundreds of prevalence surveys available in asthma, and the thousands of studies available on the distribution of cancer, cardiovascular or other major diseases. There are even fewer studies available on the social and economic cost of COPD.

Fortunately, a number of initiatives are currently underway to change this discouraging state of affairs. In particular, major steps have been taken towards this end, including the following: 1) the agreement on spirometry thresholds of diagnosis and severity by the 2003 Global Initiative for Chronic Obstructive Lung Disease (GOLD) [4, 5] and the European Respiratory Society (ERS)/American Thoracic Society (ATS) 2004 guidelines on standards for the diagnosis and management of patients with COPD [6]; 2) the establishment of

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the Burden of Obstructive Lung Disease (BOLD) initiative to facilitate standardised burden studies at an international level; and 3) the ongoing discussions to set up large, long-term cohorts of patients to better define the natural history of COPD. These programmes, together with the dissemination of GOLD in >70 countries, are helping to spread a more positive message about COPD and raise awareness of its importance.

This International Research Workshop on the Global Burden of COPD was organised with the aid of an unrestricted grant from GlaxoSmithKline R&D (Greenford, Middlesex, UK). The current authors were able to convince >30 researchers, most of them with an international reputation in COPD epidemiology, health economics and related areas of research, to share their experiences and vision about COPD in Vancouver, Canada. The success of the workshop was guaranteed by the quality and diversity of its speakers from five continents. The participants were from the World Health Organization (WHO), GOLD, ATS and ERS, and included cancer and cardiovascular epidemiologists. The programme was divided into three main sessions: burden; natural history and surrogates; and policy. Each speaker provided a mini-paper summarising his/her presentation. The current authors would like to sincerely thank the *European Respiratory Journal* for considering and disseminating these proceedings. Finally, a sad note is required. Professor Romain Pauwels was supportive of this workshop from its conception and aimed to participate actively. However, he was unable to attend due to his fragile health and finally passed away on January 3, 2005. It is to his tireless effort to fight lung disease with an international, scientific-evidence approach that these proceedings are dedicated.

COPD has been a major public health problem during the twentieth century and will remain a challenge for the foreseeable future. Indeed, even if all smokers quit smoking today, the toll of COPD would continue for several generations, since there are so many people worldwide who are already afflicted. COPD epidemiology, or the study of COPD and its determinants at the population level and its partner discipline, outcomes research, or the study of costs by quantifying the burden of COPD to society and comparing it with other diseases will show their true value if a collaborative, multidisciplinary action is undertaken.

WORLDWIDE EPIDEMIOLOGY OF COPD AND BOLD

Summary

Worldwide, COPD is in the spotlight, since the high prevalence, morbidity and mortality present challenges for healthcare systems. The inconsistent use of terminology for COPD, and the lack of widely accepted diagnostic standards for the diseases that are included in the coding within the COPD spectrum have contributed to the inaccuracy of mortality data for COPD. The approach of using the single term COPD (rather than individual coding for chronic bronchitis, emphysema and chronic airway obstruction) is being championed in global and national guidelines, with the expectation that this will improve awareness, simplify the coding and, ultimately, lead to greater accuracy in death certification for COPD. In 2000, there were more deaths in the USA from COPD among females than males. In contrast to the trend for cardiovascular diseases, death rates from COPD have been rising steadily over the past few decades. This striking increase in COPD as a cause of death is projected to occur because of the worldwide epidemic of smoking, and the changing global demographics where more people in developing countries are living longer and, therefore, are at risk of COPD for longer. Prevalence estimates may vary widely depending on which spirometric criteria are used. The BOLD initiative, which is a programme designed to provide strictly standardised, rigorous and practical methods for estimating the prevalence and social and economic burden of COPD, is described.

Introduction

Attention is being focused on COPD worldwide because it has become clear that it is an under-recognised, under-diagnosed and under-treated disease. COPD is estimated to become the third leading cause of death worldwide by 2020. The increase in mortality and morbidity from COPD is occurring worldwide as a result of both the epidemic in tobacco use and, especially in developing countries, the changing age structure of populations. This trend will continue, even if all efforts to stem the tobacco epidemic are successful. In the USA and Canada, the number of COPD deaths in females recently outnumbered the number of deaths in males. This statistic demands attention, since COPD has traditionally been thought of as predominantly affecting males. It is likely that this trend will soon be seen in other Western countries, since females are living longer and have smoked in increasing numbers since about 1940.

COPD prevalence is generally higher than is recognised by health authorities [4, 5]. Few population-based prevalence surveys have been carried out, and prevalence estimates have often relied on expert opinion or self-reported doctor diagnosis, a notoriously unreliable source of information for COPD. For example, in the USA National Health and Nutrition Examination Survey III, 70% of those with airflow obstruction had never received the diagnosis of COPD [7]. The IBERPOC study in Spain also reported that there was no previous diagnosis of COPD in 78% of identified cases and, even more worrisome, only 49% of those with severe COPD were receiving some kind of treatment for COPD [8]. Recently, the Nippon COPD Epidemiology (NICE) study in Japan, also presented within the current series, had a similar finding [9]. During the 1990s, asthma surveys successfully identified huge variations in asthma prevalence, both in children and adults, as high as 20-fold. It appears that the geographical distribution of COPD is more homogeneous than asthma, at least in the developed countries. It seems likely that the distribution of COPD follows the distribution of its risk factors very closely, of which smoking is undoubtedly the most important worldwide.

COPD is in the spotlight worldwide, as the high prevalence, morbidity and mortality present challenges for healthcare systems. From the patient's perspective, it is also a disease that has a profound effect on quality of life [10]. The burden of COPD can be assessed in a number of ways, including the following: mortality; morbidity; prevalence; disability-adjusted life yrs; cost; and quality of life. A number of authors have comprehensively reviewed this topic in detail elsewhere [11, 12]. Due to space restrictions, this paper focuses on mortality, morbidity and prevalence, with a particular emphasis on prevalence.

Worldwide mortality and morbidity from COPD

Of all of the descriptive epidemiological data available for COPD, mortality data are the most readily accessible. Inconsistent use of terminology for COPD, and the lack of widely accepted diagnostic standards for the diseases that are included in the coding within the COPD spectrum have contributed to the inaccuracy of mortality data for COPD [4, 5]. For example, the International Classification of Diseases (ICD)-9 codes used for COPD include: chronic bronchitis (ICD-9 491); emphysema (ICD-9 492); and chronic airway obstruction (ICD-9 496). Asthma (ICD-9 493) should not be included in the COPD definition. The approach of using the single term COPD is being championed in global and national guidelines, with the expectation that this will improve awareness, simplify the coding and, ultimately, lead to greater accuracy in death certification for COPD. For the next iteration of the ICD coding, the consolidation of emphysema, chronic bronchitis and chronic airway obstruction will be an important step towards obtaining more accurate data on the distribution of COPD worldwide.

Death rates from COPD have been rising steadily over the past few decades. This trend is particularly striking, since it is opposite to the trend for cardiovascular diseases, the most common chronic diseases. In the period of 1965–1998, death rates from coronary heart disease in males in the USA dropped 59%, and deaths from strokes and other cardiovascular diseases decreased 64% and 35%, respectively. Over the same period, deaths from COPD increased by 163% [4, 5].

COPD has traditionally been thought of as a disease of elderly, smoking males. It was, therefore, surprising to see that, in 2000, there were more deaths in the USA from COPD among females than males [13]. Although the rates of death were still higher in males than in females, it reflected the different age structure of the USA population for both sexes, with females living longer and, therefore, being more at risk of developing COPD. This dramatic change in the sex distribution of mortality is likely to be seen in other countries that have been lagging behind the USA in smoking patterns among females, but have been catching up over the past few decades. It is worth noting that in all countries but three (Norway, Sweden and New Zealand), and in these ones only since 2003, females have never smoked as much as males [14].

COPD mortality is not only increasing in developed countries. Worldwide, COPD was the sixth leading cause of death in 1990, and presently is the fifth. The Global Burden of Disease (GBD) Study projects that, by 2020, COPD will become the third leading cause of death worldwide [2]. The methods of the GBD Study, and its COPD results, are discussed in this issue in detail [15].

This striking increase in COPD as a cause of death is projected to occur because of the worldwide epidemic of smoking and the changing global demographics, with more people in developing countries living longer and, therefore, being at risk of COPD for longer. A recent United Nations report projected that the number of people worldwide aged >60 yrs will nearly double over the next 50 yrs, and, by the mid twentieth century, the population aged >100 yrs will be 15 times higher than today [16]. It is actually the changing demographics worldwide that is driving the COPD tidal wave even faster than the increase in smoking worldwide [14]. Not surprisingly, there are large differences across countries in COPD mortality rates, as illustrated in the recent ERS European Lung White Book [17]. Given the well-established inaccuracy when coding COPD as a cause of death, these figures must be taken as rough estimates. Males consistently have higher COPD death rates than females in all countries.

Morbidity assessment includes physician visits, emergency department visits and hospitalisations. COPD morbidity data are often less reliable than mortality, since the various ways of measuring morbidity are more prone to external factors, such as the availability of hospital beds, local and regional use of filters from primary to secondary care, the coding for utilisation being affected by reimbursement patterns, and other such potentially biasing factors. Despite these external factors, morbidity for COPD is important to track, since these data can provide an estimate of the need for health services [10, 11].

COPD prevalence

Whatever the disease, prevalence estimates depend on the definition that is used for diagnosis. For COPD, a number of different approaches have been used, including the following: doctor diagnosis; diagnosis based on the presence of respiratory symptoms; and a diagnosis based on the presence of airflow limitation (without or with a bronchodilator test as recommended by GOLD). These different approaches, not surprisingly, give very different estimates, with doctor diagnosis giving the lowest estimate of prevalence [18], diagnosis based on respiratory symptoms giving the highest estimates, and a diagnosis based on spirometry giving an intermediate estimate [13]. Since the GOLD guidelines were published, the need for spirometry in making the diagnosis of COPD has been generally accepted, and this has now become the ''gold standard'', at least for epidemiology. However, even when using so-called objective measurements, estimates may vary widely depending on which spirometric criteria are used [19, 20]. GOLD recommends that a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <70% confirms the diagnosis of COPD, and FEV_1 provides a way to stage COPD. For instance, stage 1, or mild COPD, is defined as a post-bronchodilator FEV_1/FVC ratio <70% together with an FEV_1 >80% predicted, all based on predicted (or reference) values based on sex, age and height (table 1). The same spirometry thresholds have recently been adopted by the 2004 ERS/ATS COPD guidelines [6]. Use of other criteria, such as a pre-bronchodilator FEV_1/FVC ratio or FEV_1 % predicted without the FEV_1/FVC ratio, or other thresholds, will give very different estimates [21].

An example of the importance of using spirometry to estimate the prevalence of COPD is highlighted by the recent NICE Study, a multicentre study carried out in Japan using standardised methods [9]. National statistics in Japan estimated COPD prevalence as 0.3%. Estimates based on spirometry in the NICE Study estimated COPD prevalence as 8.5% in those aged >40 yrs, almost a 30-fold difference. The NICE Study also highlights the value of using prevalence estimates to drive the awareness of COPD as an important public health problem.

TABLE 1 Diagnosis and staging of chronic obstructive pulmonary disease (COPD)[#]

Severity	FEV1/FVC %	FEV1 % pred
At risk[¶]	>0.7	>80
Mild COPD	<0.7	>80
Moderate COPD	<0.7	50–80
Severe COPD	<0.7	30–50
Very severe COPD	<0.7	<30

FEV1: forced expiratory volume in one second; FVC: forced vital capacity. All values are based on post-bronchodilator FEV1. [#]: recommended spirometry thresholds of Global Initiative for Chronic Obstructive Lung Disease 2003 [5] and American Thoracic Society/European Respiratory Society COPD guidelines 2004 [6]; [¶]: patients who smoke or have exposure to pollutants, have cough, sputum or dyspnoea, or have a family history of respiratory disease.

Up to 2002, only 32 studies had been published on the distribution of COPD prevalence [3], which is an appallingly low number. Figure 1 illustrates the chronological sequence of these studies and the prevalence estimates that they report. It would appear that there was a relative disinterest in COPD prevalence during the period of 1960–1990, followed by a steep increase in interest. It is also apparent that there is a wide divergence of prevalence estimates across the studies. Much of this can probably be attributed to different diagnostic and ascertainment methods used in the surveys.

Burden of obstructive lung disease

The lack of accurate population-based estimates of COPD prevalence in most countries prompted the formation of the BOLD initiative in 2002 by a group of investigators at the Kaiser Permanente Center for Health Research (Portland, OR, USA). BOLD is designed to provide strictly standardised, rigorous and practical methods for estimating the prevalence, social and economic burden of COPD. The data obtained from BOLD will enable governments and the private sector to make policy decisions on how to provide adequate and appropriate care for those suffering from COPD.

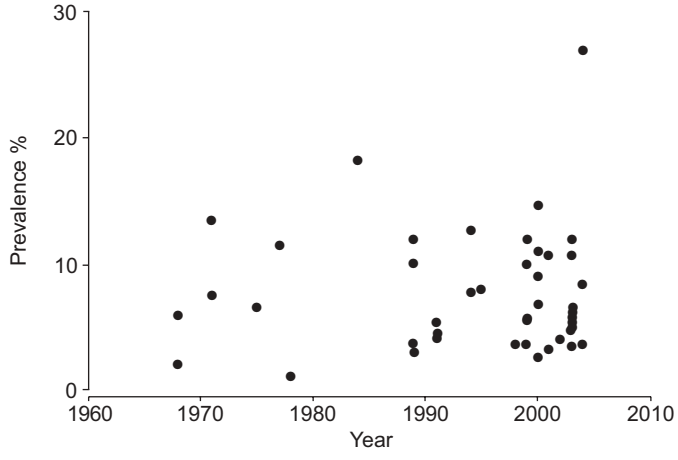

FIGURE 1. Chronic obstructive pulmonary disease prevalence surveys by year of publication.

The primary objectives of BOLD are to: measure the prevalence of COPD and its risk factors in various countries around the world; estimate the burden of COPD in terms of its impact on quality of life, activity limitation, respiratory symptoms and use of healthcare services; and develop a validated model to project future burden of disease for COPD. BOLD also seeks to determine the extent to which variations in risk factors contribute to variations in the prevalence of COPD. Recognising the importance of standardising methods worldwide, BOLD worked collaboratively with PLATINO, an initiative of the Latin American Thoracic Society, to develop the methods. PLATINO subsequently used these methods to estimate COPD prevalence in five Latin American countries, *i.e.* Brazil, Mexico, Uruguay, Chile and Venezuela [22]. The methods were piloted by BOLD in two countries: China and Turkey. Lessons learned from these pilots were incorporated into the BOLD methods after the pilots. The methods are now available for implementation worldwide, and BOLD is presently enrolling countries for implementation of the methods in 2005 and 2006.

The emphasis in BOLD is on building rigorous quality into the methods. An operations centre, located at the Kaiser Permanente Center for Health Research, supervises all aspects of the protocols. This includes sampling strategies, recruitment, translation of survey instruments, fieldwork, and data transfer and analysis. BOLD is designed primarily as a COPD prevalence survey among noninstitutionalised adults aged $\geqslant$40 yrs. This may take the form of, for example, a simple random sample, a stratified random sample, or some form of cluster sample. Countries must have their sampling plan reviewed and approved to ensure that the sample has good generalisability. Participating sites are expected to recruit a minimum of 300 males and 300 females in this age range. The proposed sample size of 600 individuals is designed to provide an acceptable level of precision for estimating prevalence at any given site.

The single most important outcome measure obtained as part of the BOLD protocol is spirometry before and after administration of an inhaled, short-acting bronchodilator. This is being carried out as the present diagnostic criteria for COPD use post-bronchodilator values for FEV1 and the ratio of FEV1/FVC%. Although standardised methods for performing spirometry are available and widely used, no single standard is universally applied. Proper training and ongoing quality control are essential in obtaining consistent high-quality measurements over time. The methods developed for BOLD meet or exceed the ATS standards for acceptable equipment and technique [23]. An ongoing quality-control process that reviews every spirogram allows for early recognition of technical and technician-related problems, and pinpoints the nature of the deficiency, for example, difficulty in getting the participants to empty completely or blow hard enough. Therefore, the identified problems can be corrected quickly and field staff who are not capable of obtaining consistent high-quality spirometry can be deployed elsewhere. These methods were developed assuming that testing will often be

done in the field, *i.e.* not in a climate-controlled pulmonary function laboratory. To optimise quality control in the BOLD study, sites are required to use the same spirometer. The spirometer used in the BOLD surveys (EasyOne™ Spirometer; ndd Medizintechnik AG, Zurich, Switzerland) was selected as it provides a high degree of accuracy, robustness, portability and storage. Also, it can be used easily in the field and where there is no electric power available, since it operates on batteries. All spirograms for the BOLD survey are reviewed at a spirometry-reading centre in Salt Lake City (UT, USA) under the direction of R. Crapo and R. Jensen (Pulmonary Division and Department of Medicine, LDS Hospital and University of Utah, Salt Lake City, Utah, USA). Data that have been reviewed and graded are returned to the country site so that they can be used for field ongoing training of the staff.

In addition to spirometry, study participants are administered a standardised questionnaire covering respiratory symptoms, health status, activity limitation and exposure to potential risk factors, such as tobacco smoke, occupational risk factors and biomass exposure. All questionnaires are forward- and back-translated, again using standardised methods to ensure comparability of the questionnaires in all countries.

All data from the field sites are transmitted through secure, encrypted Internet transfer to the operations centre. Use of the same type of spirometer and software throughout the project makes training more efficient, and data compilation and transfer easier and less susceptible to mistakes. BOLD uses a ''train the trainer'' approach to training country staff. This entails having the key staff in each country attend a 5-day training programme, which includes all aspects of the BOLD protocol. The trainers then have the responsibility of training their field teams. Quality-control surveillance, especially of the primary outcomes, allows ongoing monitoring of the field staff.

An additional part of the BOLD initiative is the development of an interactive, web-based model to estimate the economic burden of COPD. This model, once completed, will be accessible to all on the BOLD website, so that country-specific estimates of the prevalence and economic burden of COPD can be developed. Preliminary data from BOLD in the PLATINO countries [24] and in the Chinese and Turkish pilot studies are of great interest. BOLD is now entering phase 3, in which interested countries can apply to participate (www.boldcopd.org).

In conclusion, COPD is a huge and growing burden worldwide as a result of the changing demographics of the populations in developing countries and the tobacco epidemic. Better descriptive data on the prevalence, morbidity, mortality, and social and economic burden of COPD are urgently needed in order to focus the attention of the healthcare community and planners on this growing problem. Attention must also be paid to the development and acceptance of standardised methods that can be used worldwide to accumulate these data. Interventions that are appropriate for each country should be developed so that the trend can be reversed and COPD can, ultimately, be prevented and treated.

SURVEILLANCE OF COPD: LESSONS FROM CANCER

Summary

COPD was the sixth most common cause of death worldwide in 1990 and is projected to become the third most common cause by the year 2020. The global increase in deaths from chronic lung disease has provoked discussion among COPD researchers about the adequacy of current structures for monitoring the disease burden from COPD in the absence of population-based registries. In the current paper, selected insights gained from cancer surveillance over the last half-century that may be relevant to COPD surveillance are discussed. In particular, the current authors consider the goals of surveillance of noncommunicable disease and describe examples of how routinely collected mortality data from death certificates or incidence data from population-based registries can be used to monitor temporal trends, identify high-risk geographical or demographic subgroups, and focus disease-control activities. Several barriers that may impede efforts to establish population-based registries for COPD are identified. Finally, approaches that may strengthen ongoing efforts to monitor and reduce the disease burden from COPD are suggested.

Introduction

COPD was the sixth most common cause of death worldwide in 1990, but is projected to become the third most common cause by the year 2020 [25]. COPD is already ranked fourth as a cause of death in economically developed countries [26]. COPD and diabetes mellitus are the only two common conditions for which the age-standardised death rate increased in the USA during the 1990s [27]. Mortality from COPD continues to increase in many other developed and developing countries due to ageing of the population and the global spread of cigarette smoking [28]. Appropriate labelling of undiagnosed COPD patients or at the time of death, and more recognition of the disease worldwide will probably contribute towards increased COPD awareness.

The increase in deaths from chronic lung disease has raised questions about the adequacy of surveillance data currently available to monitor COPD, given the importance of the disease. This discussion will include lessons learned from cancer surveillance over the past half-century and how insights from cancer surveillance may help to inform efforts to improve surveillance of COPD. To address this, members of the American Cancer Society (ACS) will first consider the overall goals of disease surveillance, as they relate to both communicable and noncommunicable diseases. Examples will then be provided of how mortality data collected from death certificates, and incidence data from population-based registries can be used to monitor temporal trends, identify high-risk geographical or demographic subgroups, and focus disease-control activities. Several challenges or barriers that may impede efforts to establish population-based registries for COPD are identified. Finally, approaches that may help to strengthen future surveillance efforts are suggested.

Goals of disease surveillance

The Dictionary of Epidemiology defines disease surveillance as ''the continuing scrutiny of all aspects of occurrence and spread of disease that are pertinent to effective control'' [29]. An essential feature of such activities is the application of information gained from surveillance activities to strengthen disease-control efforts. While the methods and terminology that apply to surveillance of noncommunicable diseases (*e.g.*

cancer or COPD) differ somewhat from those used to monitor infectious diseases, such as malaria or HIV infection, the fundamental purpose is the same. The goal is to measure the burden of disease in well-defined populations (in terms of incidence, prevalence, survival, disability, mortality, economic costs, *etc*.) and then to use this information to improve disease control.

Examples of use of mortality data

Routinely collected information from death certificates has been useful in monitoring temporal trends in age-standardised death rates from cancer (all sites combined, or specific cancer sites) and for identifying geographical areas and demographic subgroups at a particularly high risk. Mortality data have been collected across the USA since 1930; considerable attention has been devoted to establishing systematic rules for coding cancer as the underlying or contributing cause of death to allow temporal and geographical comparisons. One use of mortality data is illustrated in figure 2, showing temporal trends in the age-standardised death rate (per 100,000 per year) from selected cancers among males and females in the USA from 1930 to 2001, the most recent year for which data are available. This figure illustrates that lung cancer has dominated cancer death rates among males in the USA since 1950, and among females since the 1980s. It also depicts the decrease in the age-standardised death rate that has occurred since 1990 for cancers of the lung, prostate and colorectum in males, and cancers of the breast and colorectum in females [30, 31]. This figure has been updated annually by staff at the ACS since the 1960s. When combined with the temporal trend in per capita cigarette consumption, it provides an impressive visual display of how the lung cancer epidemic parallels the rise and fall of cigarette consumption in the USA, as it does in many other countries.

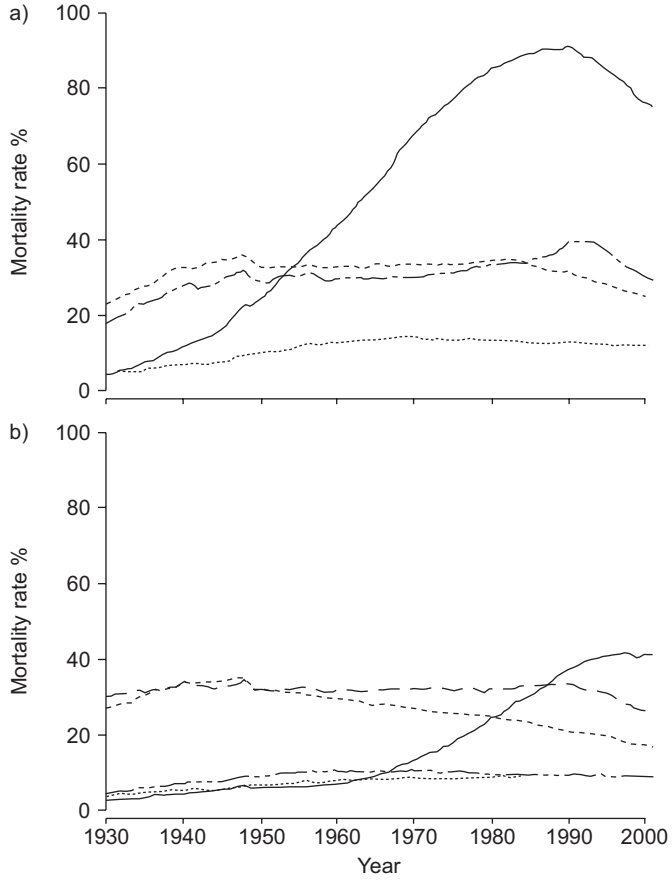

FIGURE 2. Cancer mortality rates during the period 1930–2001 for a) males and b) females. The data are age adjusted to the 2000 USA standard population. ——: lung; -----: colon and rectum; — · —: prostate; ……: pancreas; – – – –: breast; — -- —: ovary. Reproduced with permission from American Cancer Society publications.

In certain respects, the temporal trend in cancer mortality rates can provide a more reliable indication of the actual trend in disease occurrence than is provided by incidence data. Death rates are less susceptible to fluctuate with the introduction of new diagnostic or screening tests than incidence rates. This point can be illustrated by comparing the trend in incidence with that in mortality for all cancers combined in the USA during the early 1990s [31]. A large increase in the incidence rate of all cancers combined from 1973 to 2001 is seen among males in the early 1990s, followed by an equally abrupt decrease. The increase coincided with the widespread introduction of prostate-specific antigen (PSA) testing, and the decrease occurred when PSA testing reached equilibrium in the population. The introduction of PSA testing had minimal impact on the death rate from prostate cancer or all cancers combined, and no effect on the incidence or death rate from cancer in females. However, its effect on cancer incidence in males provides a remarkable illustration of how the introduction of a new, sensitive method of disease detection can distort the apparent temporal trend in incidence in a population where subclinical disease is common.

The geographical distribution of mortality from certain cancer sites can be used to identify high-risk subgroups and to target intervention efforts. For example, the death rates from cervical cancer have been mapped by state economic area among White females in the USA from 1970 to 1994 [32]. Areas with the highest death rates from cervical cancer are concentrated in Appalachia and in Southwest Texas, where widespread poverty and cultural factors limit access to effective screening tests, such as Papanicolaou (Pap) testing. Evidence that mortality from cervical cancer remained high in large areas of the USA, coupled with survey data demonstrating low utilisation of Pap testing among females in lower socioeconomic groups, helped to motivate the Breast and Cervical Cancer Early Detection Program. This initiative provides mammography and Pap testing to females who would otherwise not have access to standard screening tests.

Another example of how geographical patterns in cancer mortality can stimulate potentially important hypotheses is illustrated by a map contrasting mortality from lung cancer with that from COPD. Figure 3 shows that the age-standardised death rate from lung cancer among White males during the period of 1970–1994 was highest in the tobacco-growing states of southeastern USA [32, 33]. In contrast, areas with the highest mortality from COPD among males in the USA are concentrated in Western mountain states (fig. 4) [33]. A similar difference in the geographical patterns is seen among females. Figure 5 shows that the highest lung cancer death

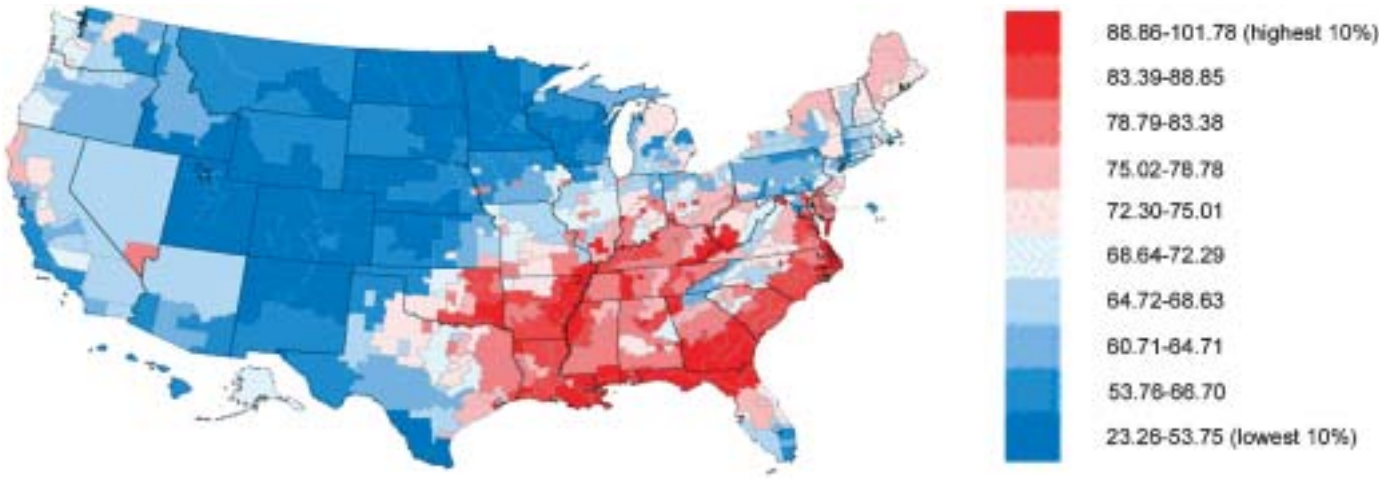

FIGURE 3. Cancer mortality rates (lung, trachea, bronchus and pleura) by state economic area (age-adjusted 1970 USA population) for White males during the period 1970–1994. Modified from [32].

rates among USA females are on the East and West coasts (as well as in Nevada), whereas the areas with highest COPD mortality include Colorado, Wyoming and other mountainous areas (fig. 6) [33].

The current authors considered several factors that might contribute to the divergent geographical patterns in mortality from lung cancer and COPD, given that tobacco smoking is a major cause of both diseases. Migration patterns among patients who develop COPD seem unlikely to explain the observed pattern. However, immigration of ethnic minorities to different parts of the USA might also affect the rates observed, as some races might be more prone to lung cancer, or COPD, than others and time of migration might impact upon risks of cancer. Occupational exposures to cofactors, such as silica from hard rock mining, or grain dust from farming might possibly contribute to the geographical pattern in males, if not females. A more plausible alternative explanation may be that pulmonary dysfunction is more likely to be recognised in regions with higher altitude and lower ambient oxygen concentration.

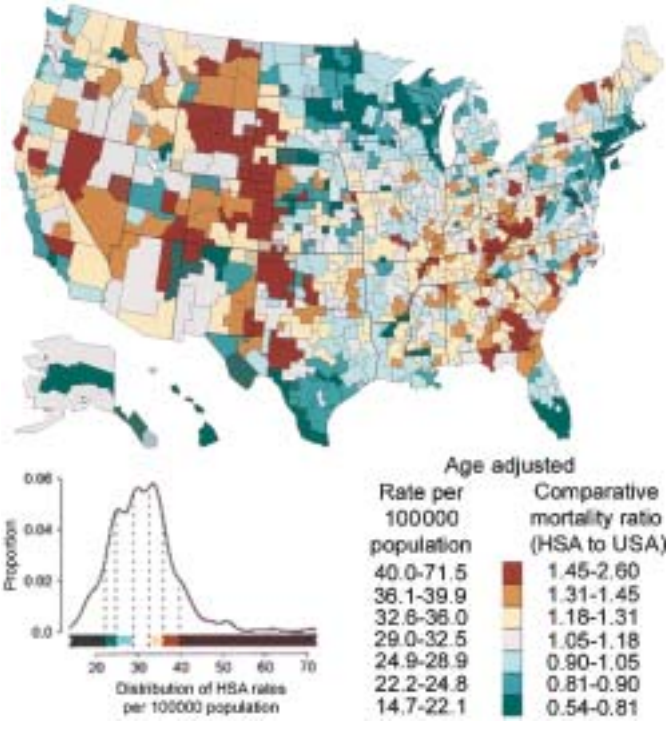

FIGURE 4. Age-adjusted death rates from chronic obstructive pulmonary disease for White males during the period 1988–1992. HSA: Health Services Areas. Modified from [33].

Descriptive analyses of temporal or geographical patterns of disease are useful in generating potentially valuable hypotheses, but not in determining the reason(s) for such patterns. More definitive answers can be obtained only from other study designs. However, descriptive analyses can reflect fundamental characteristics of underlying disease processes. For example, figure 7 compares age-specific death rates from lung cancer and COPD among males and females in the USA from 1997 to 2001 [30]. The death rates from both diseases increase markedly with age; however, the increase at older ages is even greater for COPD than for lung cancer. A decrease in the death rate from lung cancer is seen at older ages, and is believed to reflect incomplete diagnosis of lung cancer in the elderly and lower death rates among birth cohorts who preceded the era of maximum cigarette smoking in the USA [34]. In contrast, the death rate from COPD continues to increase with age. Progressive loss of lung function occurs with ageing. The development of symptoms in the elderly may lead to pulmonary function testing and documentation that an individual meets the functional criteria that define COPD. It is interesting, in light of the geographical difference between COPD and lung cancer mortality discussed previously, that the death rates from these two diseases are more strongly correlated in persons aged <60 yrs than in those >60 yrs. The correlation coefficient between the death rate from lung cancer and that from COPD, during the time period 1997–2001 across all 50 USA states, was higher among males aged

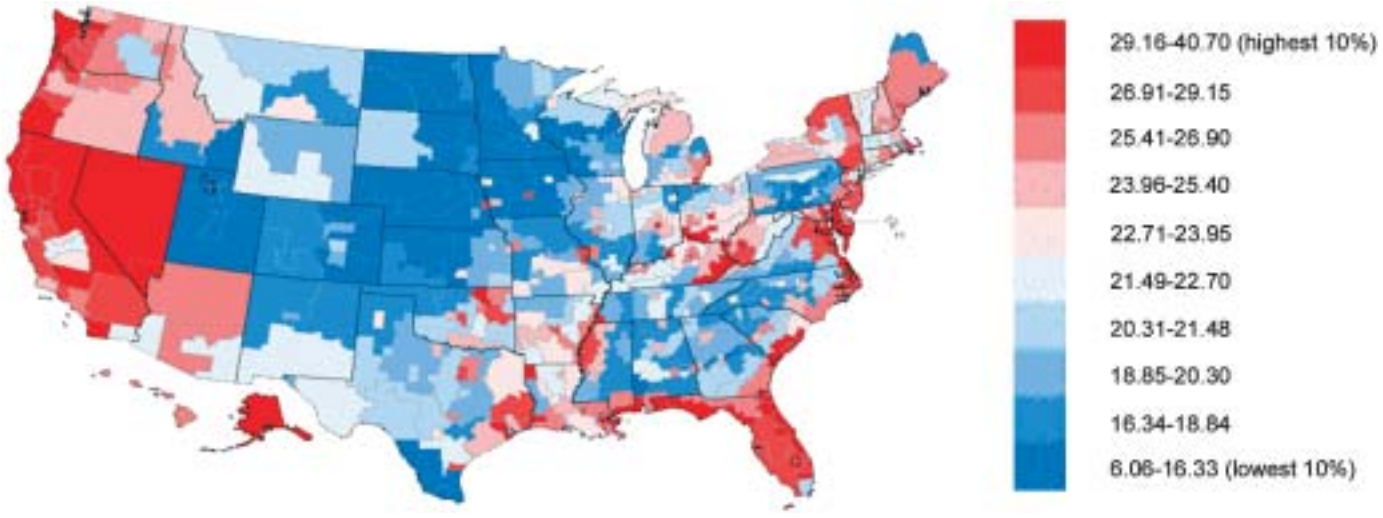

FIGURE 5. Cancer mortality rates (lung, trachea, bronchus and pleura) by state economic area (age-adjusted 1970 USA population) for White females during the period 1970–1994. Modified from [32].

30–59 yrs (r=0.61; p=0.002) than among males aged ⩾60 yrs (r=0.42; p<0.001) [27]. This suggests that at least some of the geographical differences in mortality from lung cancer and COPD may reflect factors that influence diagnosis at older ages.

Value of incidence registries

Population-based cancer incidence registries are used to monitor the number and rate of new diagnoses, to examine histological and other subtypes of disease that cannot be

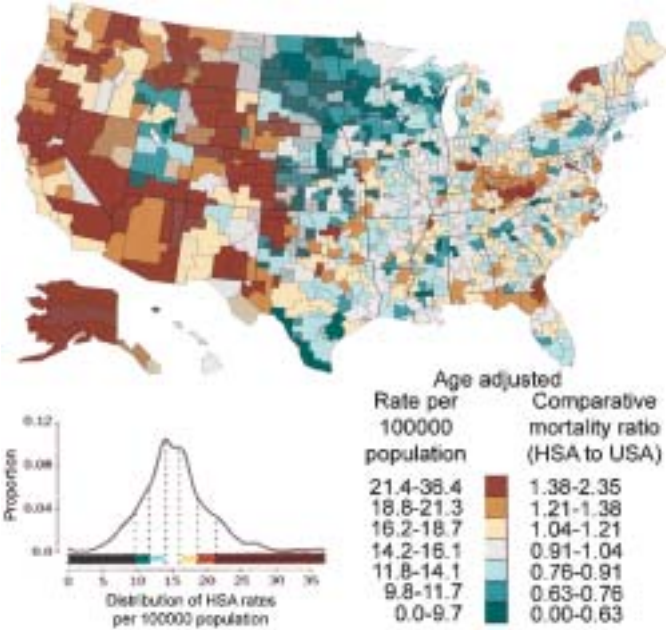

FIGURE 6. Age-adjusted death rates from chronic obstructive pulmonary disease for White females during the period 1988–1992. HSA: Health Services Areas. Modified from [33].

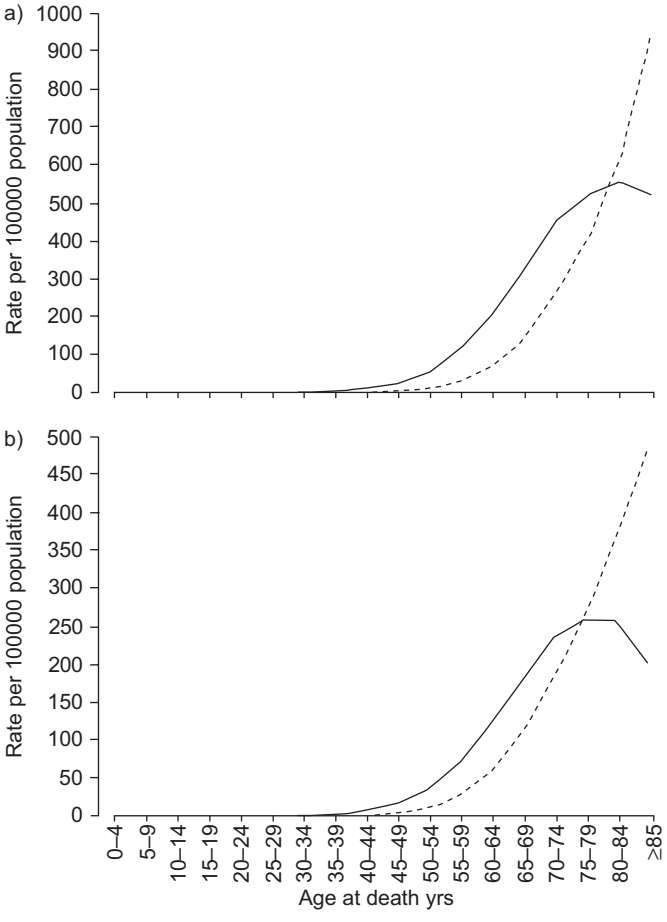

FIGURE 7. Age-specific death rates from lung cancer (——) and chronic obstructive pulmonary disease (--------) during the period 1997–2001 for a) males and b) females. Reproduced with permission from American Cancer Society publications.

identified on death certificates, and to collect information on other parameters, such as stage at diagnosis, tumour grade, and absolute and relative survival rates. The National Cancer Institute (NCI) supports a network of tumour registries called the Surveillance, Epidemiology, and End Results (SEER) Program [35]. SEER registries were established in Connecticut, Hawaii, Iowa, New Mexico, Utah, and the metropolitan areas of Detroit and San Francisco-Oakland as early as 1973. The SEER network has been expanded, subsequently, to include the 13 counties of Seattle-Puget Sound, the metropolitan area of Atlanta and 10 rural Georgia counties, Native American populations in Arizona and Alaska, and all of California, Kentucky, Louisiana and New Jersey [35]. More recently, many other states, not included in the SEER Program, have developed state-wide cancer registries through the National Program of Cancer Registries, supported by the Centers for Disease Control (CDC) [36]. Most of these registries are too new to examine long-term trends, but do provide information about cancer incidence rates for more than half of the USA population [37].

Long-term trends in cancer incidence, as measured in the original SEER nine-state areas, have been used to monitor changes in the incidence of specific cancer sites and histological subtypes [38]. For example, between 1974 and 1994, the incidence of adenocarcinoma of the oesophagus increased in both White and Black males in the USA, whereas the incidence of squamous cell carcinoma of the oesophagus decreased. Among White males, the incidence rate of these two histological subtypes actually crossed over in the late 1980s, so that adenocarcinoma became the predominant histological subtype. The rise in oesophageal adenocarcinoma observed here, and in many other industrialised countries, coincides with a major increase in obesity [39, 40].

SEER data have also been used to project the future increase in the number of cancer cases that can be expected, due to growth and ageing of the population [41]. It has been projected that, if the age-specific incidence rate from all cancers combined were to remain constant from 2000 through to 2050, and the population was to grow and age according to projections by the USA Census Bureau, then the total number of cancer cases in the USA would double between 2000 and 2050 [41]. The increase would be even larger in proportionate terms for COPD than for cancer, because the population growth is greatest in the oldest age groups where COPD risk outstrips the risk of lung cancer (fig. 7).

The information on cancer incidence collected by state tumour registries can also be used to identify high-risk areas where special intervention efforts may be required. This is particularly relevant to cancer sites for which early detection improves prognosis. For example, ROCHE *et al.* [42] used information from the New Jersey State cancer registry to identify two areas within the northeastern corner of the state where an unusually high percentage of breast cancers were classified as distant-stage disease at the time of diagnosis. Contrary to expectation, the high-risk areas were surrounded by the highest concentration of mammographic facilities in the state. However, females in the high-risk areas were more likely to be foreign-born, Hispanic or African American, have lower educational and socio-economic status, and to be less proficient in English than the average citizen of New Jersey. These results suggested that poverty and barriers of language and/or culture were the probable causes of this disparity. The information contributed to the development of a Comprehensive Cancer Control Plan for New Jersey, and led to targeted educational services to overcome these barriers.

Value of collaboration and coordination

An important development in cancer surveillance in the USA is the effort to coordinate surveillance activities across multiple organisations and agencies. For the past 6 yrs, the major organisations involved in cancer surveillance have published an annual report to the nation on the status of cancer [41, 43–47]. Organisations that collaborate on this effort include the ACS, CDC, NCI and the National Association of Central Cancer Registries. Another forum that encourages collaboration is the National Coordinating Council for Cancer Surveillance, which includes representatives from all of the previously mentioned organisations plus the American College of Surgeons, the American Association of Central Cancer Registrars and the Armed Forces Institute of Pathology. Its mission is to coordinate cancer surveillance activities within the USA, ensure that scarce resources are used optimally, and address issues of common concern [48].

Expanding definition of cancer surveillance

Increasingly, the framework for cancer surveillance is expanding to encompass a continuum of factors from health and primary prevention, through screening, diagnosis, treatment, quality of life, palliative care and end of life [48]. This expanded definition not only includes population-based data on individual risk factors, such as tobacco use, obesity or poverty, but it also includes social and legislative policies, such as cigarette taxes, restrictions on smoking in restaurants and workplaces, community initiatives to increase physical activity and federally funded nutrition programmes. The data being collected on tobacco are relevant to COPD as well as cancer. The information currently being collected on cancer treatment, comorbidity and quality of life is far more limited. Substantial resources and/or new technologies will be required to collect valid, population-based data on these issues.

Challenges of COPD surveillance

Several barriers must be addressed and overcome in order to improve the surveillance of COPD. One of the most important is to establish a uniform definition of COPD so that surveillance data can be compared across different regions of the world. In the past, the criteria used by the ATS [49] differed slightly from those of the ERS [50] and the WHO's GOLD [4]. Even if a single definition is agreed upon, the extent of pulmonary function testing in the population will influence the completeness of diagnosis and the interpretation of temporal trends. Furthermore, the reliance on functional rather than anatomical or pathological criteria will cause the incidence of newly diagnosed disease to fluctuate with cofactors such as infectious or environmental exposures that impair pulmonary function acutely and affect the likelihood that COPD will be diagnosed.

Another consideration that may limit the value of population-based incidence registries for COPD is that chronic lung

disease is more difficult to categorise into distinctive and mutually exclusive subtypes of disease than cancer. The same patient may exhibit characteristics of both chronic bronchitis and emphysema, even though these conditions may represent different pathological processes. Furthermore, the perception that COPD is a degenerative disease that predominantly affects the elderly may weaken public support for resource-intensive registries.

Recommendations

The next step in efforts to improve the surveillance of COPD might be to convene a working group of pulmonary epidemiologists to characterise the existing data resources and to consider the opportunities and challenges more systematically. This process might stimulate greater use of existing data. It could encourage collaboration, help to define the priorities in COPD surveillance, and clarify the rationale for new initiatives. There may be opportunities to extend research approaches that have been used for other diseases to COPD. For example, it may be possible to using existing national registries in Scandinavia to measure population-based incidence rates, or to conduct special studies comparing high-risk populations (such as in certain regions of China) to lower risk populations who have migrated from China to other countries. Well-designed, collaborative research projects could attract additional resources for the research, prevention and treatment of this important cause of human suffering.

GLOBAL ECONOMIC COSTS AND MODELLING IN COPD

Summary

In addition to understanding the epidemiology of a disease, estimates of the disease costs are important for appreciating the overall disease burden. Estimates of the economic burden of a disease are important for informing policy decisions. Health economic models can be used to estimate the future burden of disease or to understand the value of an intervention. Importantly, the cost estimates of the components of a disease are vital for developing health economic models of diseases. The focus of this section of the paper is to review the economic burden of COPD and COPD disease-state models. Published cost estimates from Spain, Sweden, the USA, the Netherlands and Italy are reviewed. Additional attention is given to the cost of exacerbations, which is an important component of the overall cost of COPD. Finally, the use of health-state models in COPD is briefly discussed and the BOLD study model is introduced.

Introduction

In addition to understanding the epidemiology of a disease, estimates of the disease costs are important for appreciating the overall disease burden. Estimates of the economic burden of a disease are important for informing policy decisions. Healthcare decision makers use information on the magnitude of costs associated with a disease and what might reasonably be expected in the future when making resource-allocation decisions. Estimates of the components of the overall healthcare costs of a disease can help decision makers target interventions where they may have the most impact on overall disease-related healthcare costs because the component is a driver of the overall burden of the disease.

The cost estimates of the components of a disease are vital for developing health economic models of diseases. Disease-state models can be used to estimate the economic burden of a disease where only certain pieces of information may be available, in addition to estimating the value of new interventions in the disease. Thus, disease-state models can serve as valuable tools for decision makers when setting policies.

In COPD, the burden of the disease has received increased attention in recent years. Population-based and individual patient costs have been reported from several populations. In addition, COPD disease-state models have been published in the literature. The focus of this section is to review the economic burden of COPD and COPD disease-state models. This section is divided into two parts as follows. The first part focuses on estimates of the cost of COPD, and methods for estimating disease costs are reviewed and estimates of COPD costs from throughout the world are summarised. In the second part, the COPD disease-state models are briefly reviewed and the BOLD health economic model is introduced.

Cost of disease

Economic cost studies of diseases are aimed at quantifying some of the effects that a disease has on both the patients themselves and society. This method has been widely used during recent years. However, in order to analyse and comprehend a pharmaco-economic study, it is necessary to focus on some essential aspects [51] as follows: 1) whether the study is based on the prevalence or incidence of the disease; 2) whether data collection will be from the ''top-down'' or from the ''bottom-up''; and 3) how the direct and indirect costs will be defined, calculated and considered.

Disease prevalence or incidence

The cost of disease in relation to its prevalence takes into account all the cases observed during a determined period of time, which is generally 1 yr. It also considers the resources used for prevention of the disease, treatment and rehabilitation. Moreover, the effects caused as a consequence of the morbidity and mortality during the year considered are usually also included in the analysis. In contrast, the cost of the disease, based on incidence cases, concentrates on new cases that have been detected during a determined year and the consumption of the resources used in these cases, from the diagnosis up to end of the disease, whether this be death or cure of the patient. This requires detailed analysis of the course of the disease, which may be qualified as micro-economic and epidemiological.

Top-down and bottom-up analysis

The first of the foci to calculate the cost of disease starts with total figures at a national level for all the diseases together and, thereafter, reaches the level at which the disease studied goes through a disaggregating process. The second focus, that of bottom-up, generally begins by taking a group of subjects with the disease analysed together as a base for the calculation and studies the consumption of resources used during the time period considered. The national total may be determined by extrapolation of the costs of this subset of the population.

Direct and indirect costs

Direct costs are those related to the detection, treatment, prevention and rehabilitation of the disease studied. Most studies of this type concentrate on the analysis of the costs incurred by the hospital, ambulatory and pharmacological care related to the disease in question. Other direct costs apart from healthcare, such as social services, are not included due to the lack of information.

Indirect costs in the area of economic evaluation refer to the morbidity and mortality caused by the disease. They measure the impact that the disease may have on national production. The most commonly used method of calculation is based on human capital in which days off work, whether due to disease or death, are transformed into monetary units by the application of the mean returns. This method has been extensively criticised. One of the reasons for the criticism is lack of inclusion of the collectives that are not integrated in the labour market, such as children, the elderly, housewives, *etc*.

Top-down estimates have been carried out on the costs generated by COPD in Spain. They were performed from statistical and epidemiological data. These studies have reported costs figures of ~€800 million annually in 1994 in Spain, including both direct and indirect costs [52]. If only healthcare resources (direct healthcare costs) for COPD patients are examined, €319 million are spent annually from the focus of prevalence [52]. To put these figures into context, it must be remembered that the population of Spain is 40 million. When incidence is the focus and the source of information is the real cost of a cohort of patients, the mean healthcare cost that a patient incurs from diagnosis to death is €27,500 [53]. On disaggregating the values of cost and survival, based on the grade of airway obstruction presented by the patients at diagnosis, it may be seen that the less advanced the disease is at the time of diagnosis, the greater the survival and the lower the cost per patient. In patients diagnosed with mild-to-moderate airway obstruction, the survival is 13.9 yrs with costs of €9,730. Conversely, the survival of patients diagnosed with severe obstruction is 10 yrs with costs of €43,785 [53]. The increasing cost associated with the advanced stage of the disease is well illustrated in a Swedish study of 212 patients with COPD. The small percentage (4%) of patients with severe disease accounted for 30% of the total costs, whereas 83% of patients with mild disease generated only 29% of costs [54].

In a micro-economic study performed in 1,510 patients with ambulatory COPD, followed over 1 yr (bottom-up), the average annual cost per patient was US$1,876 [55]. With this study, the approximate direct annual cost generated by COPD in Spain may be calculated from the focus of prevalence. If data obtained in the IBERPOC population-based epidemiological study are taken into account, a prevalence of COPD of 9% in the 40–69-yr age group is found, of which only 22% were diagnosed and received treatment of some kind [8]. In a Spanish population, a total of 270,000 subjects would be diagnosed and treated for COPD, multiplied by the annual average, resulting in an annual total of US$506.52 million in direct healthcare costs generated by COPD. This figure is greater than that obtained with the previous focus, which may be due to methodological differences, and also, in part, to differences in the management of the disease during the period of 1994–1998. It is interesting to compare the distribution of the costs estimated in both models. In the top-down calculation, the hospital costs constituted 36.3%, the expenses attributed to drugs were 42.2%, and the clinical consultations and diagnostic tests 22.5% [52]. In the study using the bottom-up focus, the hospital costs represented 43% of the total, drugs represented 40%, and consultations and complementary tests 17% [55]. In this case, it can be seen that, despite the differences observed in the absolute values between the two types of studies, the distribution of the costs is very similar between the two. If the total direct cost of COPD is divided between the total of the country population, healthcare for COPD costs each citizen US$13.32 annually. To put this figure into perspective, a study carried out in the Netherlands reported a cost of US$23 per capita in the care of asthma and COPD [56]. The differences may be due to the inclusion of asthma in the last study and a lower index of under-diagnosis in the Netherlands, among others.

In a study undertaken in the USA following the bottom-up focus in a cohort of 413 patients with COPD, direct healthcare costs were found to range from US$1,681 for patients in stage I COPD, as defined by previous guidelines [5], US$5,037 for patients in stage II and US$10,812 for those in stage III [57]. These costs are much higher than those observed in Spain and may be due to a variety of factors, among which the most important is that the patients in the North American study were selected from a population with COPD registered in the hospital, whereas the Spanish study included patients who had consulted their primary-care physicians. This may confer greater severity or complexity to the patients included in the study performed in the USA. Most probably, the difference in costs per COPD patient between the USA and Spain or other countries is largely due to the very big difference between the unit costs of days in hospital. Other studies carried out regarding the cost of COPD in different countries are shown in table 2. The importance of the origin of the population under study is remarkable. A recent Spanish study reported a direct annual cost of only €909.50, which was explained by the fact that the patients were identified in a population-based epidemiological study with most having mild-to-moderate COPD [58].

Another way of placing the cost of COPD into perspective is to compare it with the cost of asthma. Asthma has traditionally received greater investigator attention than COPD; however, the latter is more prevalent in the adult population and its healthcare load should also be greater. In another study carried out in Spain, SERRA-BATLLES *et al.* [62] determined the direct costs of asthma in 385 adult patients. The higher costs of COPD compared with asthma, particularly in the group of severe patients, is due to the higher frequency of hospitalisations.

Nonetheless, COPD also produces an increase in general healthcare costs, not only due to the pulmonary disease itself. Patients with COPD who are either current or former smokers have a frequent presentation of associated diseases and these patients receive multiple medications. Both of these characteristics lead to deterioration in their quality of life, as well as in healthcare costs [63]. In a study carried out in the USA, it was found that the use of healthcare resources was doubled in patients with COPD compared with an age- and sex-matched

TABLE 2 Comparison of the costs published on chronic obstructive pulmonary disease in different countries

First author [ref.]	Country	Focus	Costs	Cost·patient^{-1}·yr^{-1}	Global cost·yr^{-1}
Morera [52]	Spain	Top-down	Direct and indirect	€959	Direct €319 million Indirect €541 million
Hilleman [57]	USA	Bottom-up	Direct	Stage I US$1681 Stage II US$5037 Stage III US$10812	
Jacobson [59]	Sweden	Top-down	Direct and indirect		Direct €109 million Indirect €541 million
Wilson [60]	USA.	Top-down	Direct	Emphysema US$1341 Chronic bronchitis US$816	US$14500 million
Rutten van Mölken [56]	The Netherlands	Top-down	Direct	US$876	
Dal Negro [61]	Italy	Bottom-up	Direct	Stage I €151 Stage II €3001 Stage III €3912	
Jansson [54]	Sweden	Bottom-up	Direct and indirect	US$1284	US$871
Miravitlles [55]	Spain	Bottom-up	Direct	Stage I €1185 Stage II €1640 Stage III €2333	€427 million
Masa [58]	Spain	Bottom-up Cross-sectional	Direct	€909.5	€238.8 million

control group, with most of the costs being due to diseases related to smoking. Respiratory system disorders were the principal discharge diagnosis, but cases with COPD had a higher proportion of discharge diagnoses than controls in almost every major diagnosis category. Admissions for cardiovascular diseases, the leading discharge diagnosis category in controls, were almost twice as common among COPD cases [64].

The cost of exacerbations of COPD

Exacerbations and hospitalisations, in particular, constitute the most important direct healthcare costs associated with COPD. The economic impact of COPD in 1993 was estimated to be >US$15.5 billion in the USA, US$6.1 billion of which corresponded to hospital stay [57]. Some studies have shown that the cost of hospital stay represents 40–57% of the total direct costs generated by patients with COPD, reaching up to 63% in severe patients [55–57]. In the USA, the mean cost of hospital admission by COPD in a cohort of patients with severe COPD was estimated to be US$7,100 [65]. Thus, the costs associated with exacerbations of COPD are remarkable.

In a pharmaco-economic study including 2,414 acute episodes of COPD treated in the outpatient clinic, it was concluded that the average direct cost of an exacerbation was US$159, but the cost of therapeutic failure, defined as the need of a new medical contact for persistence or aggravation of symptoms during the 30 days after initiating treatment, was US$477.5 [66]. Therefore, 63% of the total costs associated with the management of an exacerbation are costs derived from failure, or rather, in a hypothetical situation in which failure is reduced to zero, the average cost of treatment of an exacerbation would decrease from US$159 to only US$58.7 (fig. 8) [66]. Another study performed in Sweden on 75 exacerbations, of which 17 required either an emergency visit or admission, resulted in a mean cost of 3,163 SEK (€343.8), ranging from €13 for those managed by the patient at home and €2,375 for those that required an emergency visit or admission [67]. Therefore, costs

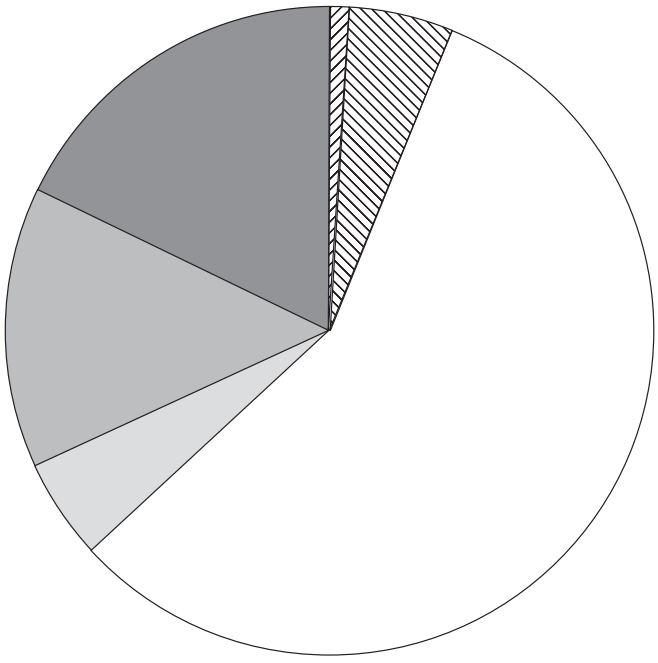

FIGURE 8. Percentage distribution of costs associated with treatment of acute episodes of chronic obstructive pulmonary disease. The diagram shows the distribution of the costs of the acute episode (■: add-on drugs (18%); ■: initial drugs (14%); ■: clinic visit (5%)) and the distribution of the costs of therapeutic failure which composes the remaining 63% (of which, ▨: new clinic visit (1%); ▧: emergency (7%); □: hospitalisation (92%)). Modified from [62].

of exacerbations are closely related to the severity of the baseline disease and the risk of admission.

Modelling in COPD

Health economic models have been used in several chronic diseases to evaluate the costs of a disease, as well as the value of new interventions [68–72]. They can serve as valuable tools for decision makers when making resource-allocation choices. Health-state models attempt to capture the nature of the disease in a mathematical form, in order to answer questions about the costs of the disease. In COPD, health-state models have been used to estimate the burden of disease and to examine the value of interventions.

COPD health-state models

Health-state models are used to model complex diseases in which the time-frame of the analysis is relatively lengthy and the probabilities of moving between health states can change over time. The model consists of mutually exclusive health states that represent the disease. Allowable transitions between health states are defined and populated with probabilities that represent the likelihood of moving between the states. Health-state models are typically presented schematically as circles for each of the health states and arrows that show all of the possible movements.

In COPD, four separate health-state models have been reported in the literature. RUTTEN VAN MÖLKEN *et al.* [56] and FEENSTRA *et al.* [73] have estimated the economic burden of COPD in the Netherlands using a COPD health-state model.

The BORG *et al.* [74] model was developed to follow the natural progression of COPD and was developed around two health-state models: acute exacerbations of COPD and disease progression of COPD.

The model developed by SIN *et al*. [75] focused on determining the value of inhaled corticosteroids for the treatment of patients with COPD. Finally, OOSTENBRINK *et al.* [76] developed a short-term COPD model that is fully probabilistic. That is, the model incorporates the uncertainty in both costs and effects of treatments of COPD when estimating the cost-effectiveness of interventions in patients with COPD. Each of these models was developed with different objectives, ranging from evaluating treatments over a short-term period to evaluating the economic burden of COPD over several years.

In addition to the COPD health-state models that have been published, two more models are recently available. SPENCER *et al.* [77] developed a COPD model that contains four mutually exclusive health states in order to evaluate the long-term cost-effectiveness of interventions for patients with COPD. Additionally, the Dutch model discussed previously has been extended to a COPD disease-state model that now includes disease progression and has been used to estimate the economic burden of COPD in the Netherlands [78]. The recent growth of the literature around disease-state models and COPD indicates the potential value of these models in estimating the burden of disease and the value of interventions in patients with COPD. In that context, the BOLD project discussed previously has included a health economic component.

BOLD economic model

The model being developed as part of the BOLD international project incorporates aspects of the model from the Netherlands, which examined population-level costs into the future, and the COPD health-state models, which evaluated disease interventions. The objective of the BOLD economic model is to provide a health policy tool that can be used to compute site-specific estimates of the current and future economic impact of COPD, as well as understand the potential impacts of disease interventions.

The model will utilise aggregate estimates from the BOLD prevalence survey and local cost and population estimates to provide a site-specific estimate of the current and future costs related to COPD. Base case analyses of the estimate of the current and future economic burden of COPD will be conducted for sites participating in the pilot phase of the project. In the base case analysis, information obtained from the prevalence survey will serve as input parameters for the economic model. The inputs will be based on sex-specific summary information. Parameters that will be used in the model include estimates of prevalence, smoking rates and healthcare utilisation rates. The cost information used in the economic model will be based on local unit cost estimates. Cost estimates for hospitalisations, physician (or other healthcare provider) visits and medications will be incorporated in the model. Additionally, estimates of incidence rates for COPD, mortality rates and smoking prevalence in younger populations will be used to determine future costs associated with the disease.

Model structure

The structure of the BOLD model is shown in figure 9. Like the model from the Netherlands, the BOLD model includes persons with COPD, as well as those at risk for the development of the disease. The arrows show the possible transitions between health states for the yearly transition period. Patients with COPD or those who develop COPD are categorised according to the GOLD staging criteria and further divided into smokers and nonsmokers. Since smoking status probably has an impact on disease progression and other outcomes, COPD health states based on smoking status were included in the model.

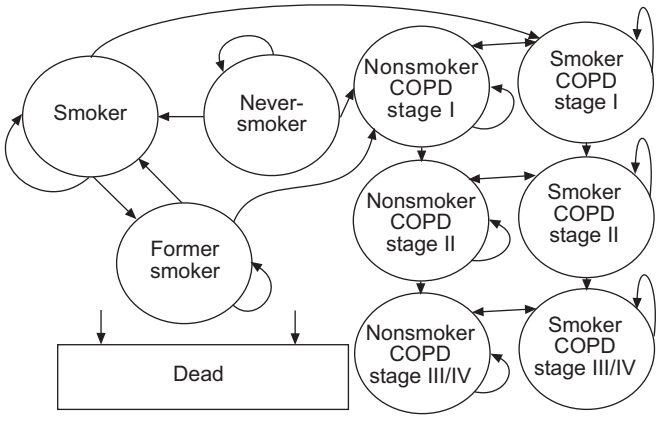

FIGURE 9. Burden of Obstructive Lung Disease health economic model structure. COPD: chronic obstructive pulmonary disease.

A key component of the model is accurately capturing disease progression as it influences estimates of future costs. Previous models have used data from the Obstructive Lung Disease in Northern Sweden (OLIN) study and the Lung Health study to determine disease-progression rates. However, the progression estimates for the OLIN study have not been published in the peer-reviewed literature and the estimates from the Lung Health study do not capture all levels of disease severity. If progression varies by disease severity, then the data from the Lung Health study will not accurately reflect the natural progression of the disease. Thus, the current authors intend to use data from the Framingham Study to empirically derive estimates of disease progression for the BOLD model.

Model output

The BOLD economic model will provide estimates on the costs related to the treatment of COPD, as well as the types of healthcare resources consumed. Estimates of the current and future costs of overall and per capita will be provided. Costs will be estimated per COPD patient and be stratified by severity. Additionally, the number of events in terms of hospitalisations, emergency department visits and outpatient visits will be reported. Finally, estimates of mortality and quality of life will be provided.

Model uses

The model is intended to provide decision makers and others with a tool to estimate the current and future economic burden of COPD in their region. The model can be used to determine which components of COPD have the most impact on overall costs. The model can be used to estimate the resources that may be required in a 10-yr period for treating COPD patients. Finally, the model could be used to evaluate the economic impact of various interventions (either real or hypothetical).

TOBACCO AND OTHER CAUSES OF COPD

Summary

Tobacco smoking is undoubtedly the most important risk factor for COPD. Smoking causes COPD more commonly than had been previously recognised, with up to 50% of long-term smokers developing the disease. However, smoking accounts for a smaller proportion of cases of COPD than previously realised, with a population attributable risk for COPD with smoking of ~50%. It appears that it is the interaction with other risk factors that determines an individual smoker's susceptibility to COPD. In addition to public health and political measures to reduce the prevalence of smoking, the investigation and modification of these other risk factors is essential if the global burden of this disease is to be reduced.

Introduction

In 1964, the USA Surgeon General's report warned that tobacco smoke was the most important cause of chronic bronchitis. The statement was expanded in the next report published in 1967, implicating tobacco in the aetiology of emphysema [79]. Since then, thousands of articles have been devoted to establishing tobacco as the leading risk factor in the development of COPD. Despite the wealth of evidence available, the exact mechanisms by which tobacco causes COPD are not yet fully understood and there remain important unanswered questions. Given the strong association, why do only 15% of smokers develop COPD, or is the incidence actually higher? What are the causes of the individual variation in response to tobacco smoke seen in smokers? What other factors play a role in the pathogenesis of COPD and are they amenable to modification?

An individual's susceptibility to COPD is determined by the interaction between ''host factors'' (*i.e.* genetics, airway hyperresponsiveness, lung growth, sex and race) and exposure to ''environmental factors'' (*i.e.* tobacco smoke, passive smoke, marijuana smoke, pollution, occupational dusts/chemicals, socio-economic status, respiratory infections and diet). In this section, the role of host and environmental factors implicated in the pathogenesis of COPD is briefly reviewed.

Genetic risk factors

There is a significant body of evidence that supports a hereditary component to the development of COPD. Clustering of COPD cases has been observed in families, and several studies have demonstrated an increased incidence of COPD in relatives of cases when compared to controls. Concordance in lung function impairment has been witnessed in monozygotic twins, but not replicated in studies on dizygotic twins [80].

Numerous genetic abnormalities have been proposed to contribute to the pathogenesis of COPD (*e.g.* α_1-antitrypsin, α_1-antichymotrypsin, cystic fibrosis transmembrane regulator, vitamin D-binding protein, α_2-macroglobulin, cytochrome P450 A1, blood group antigens, human leukocyte antigen locus and immunoglobulin deficiency). Their importance lies not only with better understanding of the mechanisms by which COPD develops, but also in identifying novel therapeutic targets for the primary or secondary prevention of COPD.

The most extensively researched of these genes is α_1-antitrypsin, a potent antiprotease, which also inhibits leukocyte elastase. Over 70 variants have been identified, of which the most common are M, S and Z with allele frequencies of 0.93, 0.05 and 0.02, respectively. In addition, there are mutations that affect the function of α_1-antitrypsin. The severity of the deficiency is determined by the genotype inherited, with the ZZ genotype having the most severe deficiency, with α_1-antitrypsin levels being ~15% of normal [80]. Homozygotes of the Z variant have a significantly accelerated decline in lung function at a young age, with a synergistic interaction with exposure to cigarette smoking. However, the overall contribution of this genotype to the global COPD burden is small [80].

Airway hyperresponsiveness, asthma and atopy

The concept that airway hyperresponsiveness may be a host factor that predisposes individuals to COPD is known as the ''Dutch Hypothesis'' [81]. It has been proposed that asthma, emphysema and chronic bronchitis are different manifestations of the same underlying disease processes and that the actual presentation depends on host factors such as age, sex, atopy and the relative severity of airway hyperresponsiveness, which modulate the response to environmental factors such as cigarette smoke. Clinical studies have also demonstrated an association between bronchial hyperresponsiveness and

COPD. What is not yet clear is whether the hyperresponsiveness seen in COPD is a manifestation of the airways narrowing or a causative factor in its pathogenesis.

The differentiation between asthma and COPD can be difficult in older adults, since a component of irreversible airflow obstruction and a reduced diffusion capacity may be features of both conditions [81, 82]. Amongst adults with obstructive lung disease, those with a diagnosis of asthma represent the largest subgroup [83]. Furthermore, longitudinal cohort studies have shown that asthma in adults aged in their late 40s is strongly associated with symptoms of chronic bronchitis, a diagnosis of emphysema, or fulfilling COPD criteria 20 yrs later. The risks are substantial, over 10-fold, when compared with nonasthmatics, even after adjusting for confounders such as smoking [84].

Similarly, there is evidence to suggest that atopy (as indicated by a raised blood eosinophil count) may have a role in the pathogenesis of COPD, independent of its association with bronchial hyperresponsiveness [81].

Lung growth in utero *and during infancy*

There is evidence that significant insults during the vital period of lung growth *in utero* (after 16 weeks) may have implications for lung function in adulthood [85]. Insults include maternal smoking, which has been shown to have several adverse effects on lung development and poor foetal nutrition. Premature babies with low birthweights have been shown to have impairment of FEV_1 that persists into late childhood. More importantly, birthweight is correlated with FEV_1 in adults and the death rate from chronic bronchitis has been shown to be inversely proportional to birthweight. Similar relationships also exist with weight at 1 yr of age, when the lungs are still developing.

Sex

The subject of sex differences in COPD is controversial, with current evidence suggesting differential sex risks for COPD in different communities. Among the possible explanations for observed sex differences are differences in lung morphology, smoking, hormonal factors, differences in inflammatory response between the sexes, and occupational confounders [86].

Tobacco smoke

Tobacco smoke is the only environmental risk factor whose contribution to COPD is undisputed, satisfying all of the Bradford Hill criteria for proving causation. Although the link between cigarette smoking and COPD is well established, there remain some areas of uncertainty in the relationship, including the basis of the wide range of susceptibility to cigarette smoke within and between populations.

The effects of tobacco smoke on the lung are multiple, including the release of elastase from inflammatory cells in the lung, oxidative stress and inactivation of α_1-antitrypsin. Of particular importance is the effect whereby tobacco smoke increases intrapulmonary elastase activity, inactivates intrapulmonary elastase inhibitors and blunts the repair of the injured pulmonary extracellular matrix [87]. Tobacco smoke is also a rich source of oxidants and upregulates pathways that decrease antioxidant capacities within the lung [88]. Through the recruitment and stimulation of alveolar macrophages and neutrophils, an acute or chronic inflammatory process is established within the lung, which leads to further tissue damage [89].

While it is generally considered that only 15–20% of smokers develop COPD, recent evidence indicates that the figure may be closer to 50% [90]. This study also suggested that the population attributable risk for COPD with smoking is ~50% rather than the 90% currently proposed. These observations suggest that COPD occurs more commonly in smokers, but is responsible for a smaller proportion of cases of COPD than previously realised. The importance of stopping smoking to reduce the progression of the disease has been well demonstrated (fig. 10) [90, 91].

Smoking remains the major cause of mortality from COPD, which has been increasing over the past two decades, in contrast with a decreasing mortality for other major chronic diseases (fig. 11) [92]. In 2000, it has been estimated that there were ~1,000,000 premature deaths in the world attributable to smoking [93].

Environmental tobacco smoke

Notwithstanding the limitations of studies investigating the association between passive smoking and lung disease, there is evidence that maternal smoking *in utero* is associated with impaired lung development and reduced lung function in adults [94]. Children living in houses in which one or more of the parents smoke have more respiratory tract infections. There is also evidence in adults that exposure to second-hand smoke is associated with reduced lung function, including impaired diffusing capacity, indicating the presence of emphysema [95]. The effects of public health measures limiting smoking in the workplace and public areas are awaited with interest.

Marijuana smoke

Compared to tobacco, marijuana has been somewhat neglected by researchers investigating the aetiology of COPD. This is

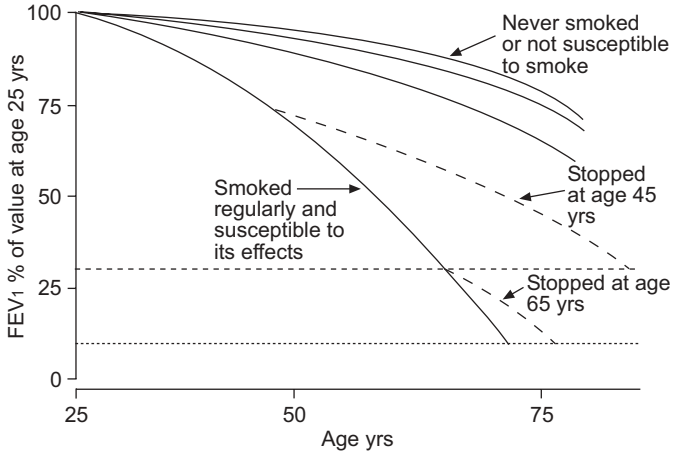

FIGURE 10. The natural history and the change over time of the forced expiratory volume in one second (FEV_1) in nonsmokers, ex-smokers and smokers. ----: disability; ....: death. Amended and reproduced with permission from the BMJ Publishing Group (*BMJ* 1977; 1: 1645–1648 [91]).

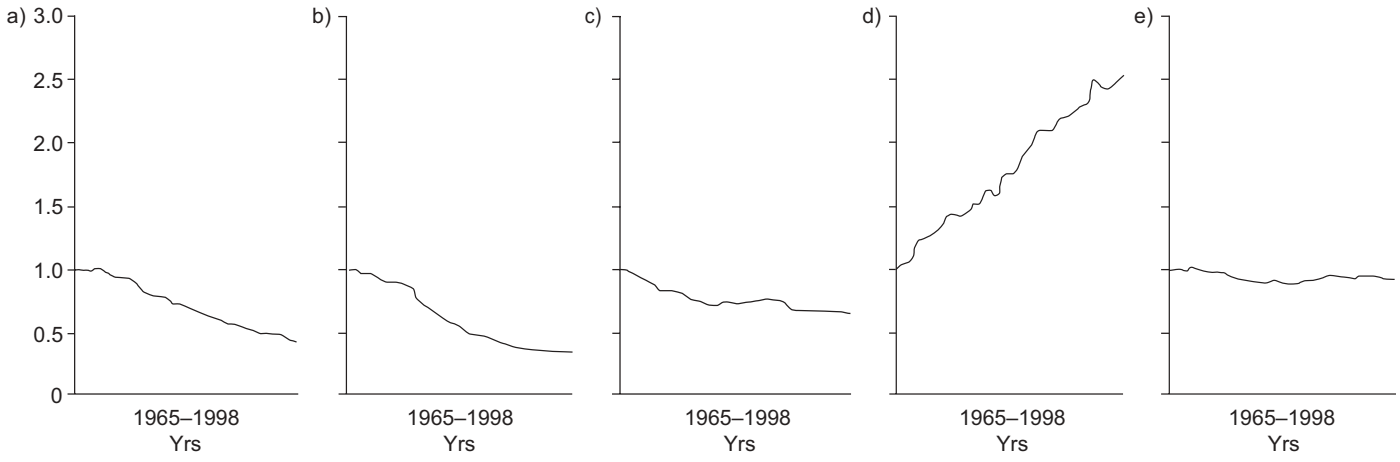

FIGURE 11. Change in age-adjusted death rates in the USA, between 1965 and 1998, for a) coronary heart disease (-59% change), b) stroke (-64% change), c) other cardiovascular diseases (-35% change), d) chronic obstructive pulmonary disease (+163% change), and e) all other causes (-7%). Adapted with permission from [5].

surprising, considering that marijuana is the most commonly used illegal drug worldwide, is constitutionally similar to tobacco (aside from the two active ingredients), is smoked without filters, and results in a four-fold greater particle burden on the respiratory tract than tobacco smoking [96]. Conversely, fewer joints are smoked by marijuana smokers than cigarettes by tobacco smokers, and, while tobacco smoking is often a lifelong habit, most marijuana smokers cease smoking in later adult life.

Since a significant number of marijuana smokers also smoke tobacco, future research needs to be directed at investigating the possibility of a synergistic relationship between the two substances. In addition, a dose equivalence with tobacco would be informative in assessing the relative risk of COPD for marijuana smokers.

Air pollution

Historically, the association between respiratory disease and pollution became apparent during the 1950s when the great ''British Smogs'' caused an acute mortality epidemic from chronic bronchitis and respiratory failure [97]. Subsequent studies from other countries confirmed these findings, demonstrating the adverse effects of air pollution on lung function in childhood and exacerbations of COPD resulting in hospital admissions and sick days due to respiratory symptoms [97, 98]. The magnitude of the role of outdoor air pollution in the pathogenesis of COPD is variable by country and geography.

Although air-pollutant emissions are dominated by outdoor sources, human exposures are a function of the level of pollution in places where people spend most of their time. Human exposure to air pollution is dominated by the indoor environment. Globally, the largest source of indoor pollution comes from cooking and heating with solid fuels, such as dung, wood, agricultural residues and coal. These fuels emit substantial amounts of pollutants. It has been estimated that indoor smoke from solid fuels causes ~20% of cases of COPD worldwide [99].

Occupational dusts/chemicals

Occupational exposure to dusts, chemicals and fumes is a risk factor in the development of COPD [100]. The agents particularly implicated with impaired lung function are silica, coal dust, fibreglass, sawdust, freons and solvents. There is a relationship between the degree of lung function impairment and the intensity and duration of exposure, which supports causality. It is likely that the interaction between occupational exposure and other risk factors determines whether an individual develops COPD [101].

Intriguingly, it has been shown that males with significant occupational exposure have greater lung function impairment if they also have a positive airway challenge test than those who do not [100]. This suggests that occupational exposure constitutes a risk factor in those who have an underlying predisposition to airways disease or, alternatively, that airway hyperresponsiveness represents a component of the airway response to injury.

Given that 10–20% of cases of COPD may be attributable to occupational exposures, occupational and public-health policy makers and clinicians need to address this potential avenue of disease causation and prevention [102, 103].

Socio-economic status

COPD is linked to socio-economic status, measured by income and educational level, in terms of severe exacerbations, prevalence and mortality. While a greater proportion of people in the lower socio-economic group smoke, this is insufficient to explain the association. The strength of the association is marked with the difference between the lowest and the highest socio-economic group equivalent to the deterioration in lung function seen in 10 yrs of ageing in nonsmokers. The reasons for the association are multiple, but may include poorer housing, poorer nutrition, use of fossil fuels without adequate ventilation, and greater frequency and severity of respiratory tract infections [104].

Respiratory infections

There is evidence to suggest that an insult inflicted on the lungs by infective agents during childhood, when the lungs are still developing, may cause permanent damage that predisposes to COPD in later life. This hypothesis arose following the observation in Great Britain that regional rates of chronic

bronchitis in adults were similar to the regional rates for respiratory illness in children [85]. Subsequent studies reported that bronchiolitis, croup and pneumonia in early childhood may cause long-term functional impairment [105, 106]. The impairment may be substantial with a mean loss in FEV_1 of 0.65 L reported in males who had pneumonia before the age of 2 yrs, a reduction in FEV_1 about twice that associated with lifelong smoking [105]. Since follow-up commences after the childhood infection in many studies, it is not clear which component of functional impairment was a result of the infection and which was due to a predisposing factor that led to the infection in the first place.

There is also evidence to suggest that latent adenoviral infection or colonisation of the airways with bacterial pathogens such as *Haemophilus influenzae* or *Branhamella catarrhalis*, or other pathogens such as *Chlamydia pneumoniae* may contribute to the pathogenesis of COPD [107–109]. The role of ongoing infection in the lower airways is also suggested by the recent findings of coincident bronchiectasis in up to half of subjects with moderately severe COPD [105].

Diet

The important contribution of oxidative stress to lung injury in COPD was the foundation for considering diet as a risk factor for the disease [88]. This led to the theory that the antioxidant properties of certain nutrients, such as vitamin C, beta carotene, selenium and copper, may modulate an individual's susceptibility to oxidative damage. It has also been proposed that a diet rich in omega-3 fatty acids may inhibit arachidonic acid production, thereby protecting against bronchoconstriction. While it has been demonstrated that a diet rich in fruit and vegetables is associated with a reduced risk of COPD [110], the effect that modification of diet has on the prevalence of COPD is yet to be determined.

In conclusion, extensive epidemiological investigation has shown that tobacco smoke is the single biggest risk factor for chronic obstructive pulmonary disease. However, it appears that it is the interaction with other risk factors that determines an individual smoker's susceptibility to chronic obstructive pulmonary disease. In addition to public health and political measures to reduce the prevalence of smoking, investigation and modification of these other risk factors is essential if the global burden of this disease is to be reduced.

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A question and answer document file following each of the manuscripts presented during the workshop is available at www.ersnet.org/elearning.

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