Lung cancer: the American view

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Bronchogenic carcinoma continues to be a major public health problem in the United States. Although there are indications of the levelling off of new cases and deaths from lung cancer in men, the rates for women continue to rise. It was estimated by the American Cancer Society that we would see 152,000 new cases in 1988: 100,000 in men and 52,000 in women [1]. The number of deaths keeps pace – 139,000 expected in 1988 – 93,000 deaths in men and 46,000 in women. Bronchogenic carcinoma remains the leading cancer killer in men, and since 1986 it is the leading cancer killer in women, having passed breast cancer. Regrettably, little has occurred in the last three decades to improve the outlook for those found to have carcinoma of the lung. Of all patients diagnosed, approximately 13% survive for 5 years, roughly the same as series published from the 1950s [1]. We know that if the tumour is localized at time of diagnosis, 33% of patients will be alive at 5 years. Unfortunately, only 24% are detected and treated at early, localized stages. These figures, too, have changed little over the past two decades.

In attempting to give an overview of the American approach to this problem, many areas of research and clinical practice might be considered. We elected to focus this presentation on two general areas. The first is screening for lung cancer in high-risk populations and especially looking at the experiences of the Cooperative Early Lung Cancer Group [2–5] sponsored by the National Cancer Institute (NCI). The second area is the broad challenge of lung cancer prevention. For this latter subject, we have drawn heavily on the writings of Dr. Peter Greenwald and Dr. Joseph W. Cullen of the Division of Cancer Prevention and Control of the NCI [6–8].

In selecting this approach, we are omitting many important aspects of diagnosis, staging, and therapy which might be addressed in a more comprehensive review of lung cancer today.

Screening for lung cancer

Although its effectiveness has been questioned, surgical resection continues to be the preferred treatment for limited stage non-small cell lung cancer [9]. The symptoms of early lung cancer are nonspecific, and by the time patients seek medical care because of symptoms, the disease is often advanced and not amenable to curative resection. Thus, in the early 1970s, attention was directed to seeking earlier recognition of early-stage presymptomatic lung cancer by screening.

The only reliable methods currently available for detecting presymptomatic lung cancer are chest radiographic examination and sputum cytologic testing. These procedures are complementary: the chest radiographic film is more useful for identifying peripheral tumours, usually of non-small cell type, and sputum tests are more likely to detect central endobronchial tumours, especially squamous cell type.
Full size, 36 cm x 43 cm, posteroanterior (PA) stereoscopic or PA and lateral films taken at 125 to 140 kV are preferred because of their sensitivity. Multiple-day pooled samples of spontaneous sputum or induced sputum collections improved sensitivity. Introduction of the flexible fiberoptic bronchoscope by Ikeda in 1968 and improved localization techniques in the early 1970s permitted better detection for occult carcinomas [10].

In 1971, the NCI began sponsorship of three large, long-term, randomized controlled trials of screening for lung cancer by using chest radiographic films and sputum cytologic tests. The trials were conducted at the Mayo Clinic, Johns Hopkins University, and Memorial Sloan-Kettering Cancer Center, with independent statistical support by the University of Cincinnati. Collectively, these participating institutions were designated the NCI Cooperative Early Lung Cancer Group [10]. The goals of the Cooperative Group were to determine: whether detection of lung cancer could be improved by adding modern cytologic techniques to either yearly chest radiographic films (Hopkins, Memorial) or chest films done every 4 months (Mayo) and whether mortality from lung cancer could be reduced significantly by this type of screening programme followed by newer localization methods and appropriate treatment [3].

At the time these clinical trials were designed it was assumed that yearly chest radiographs would not affect lung cancer mortality. There has never been a randomized controlled trial of lung cancer screening with full-size high kV chest film, either alone or combined with modern sputum cytologic tests, compared with no testing at all.

The goal of the Mayo Lung Project (MLP) was to determine whether chest radiographs and sputum cytologic tests offered periodically to a group of high-risk individuals would result in significant reduction in lung cancer death rate compared with a control population not offered regular testing, but advised to seek annual examinations. Persons at high risk were defined as men age 45 years or older who smoked one package of cigarettes or more daily. Tests were offered to the screened population at 4 month intervals for 6 years.

From November 1971 to July 1976, 10,933 Mayo Clinic outpatients were interviewed who met study requirements. None was suspected of having respiratory tract cancer at the time of entry. All received 36 cm x 43 cm stereoscopic PA chest radiographs. Not all were able to produce spontaneous sputum, but 10,117 (92.5%) submitted 3 day pooled specimens that were satisfactory for examination. All subjects received initial screening because of the clinical practice recommendations at Mayo Clinic already in place since 1970.

If either test was positive for lung cancer in the initial screening, the patient became a “prevalence” case. If both were negative, he was eligible for the prospective interval screening study. There were 91 patients with lung cancer identified in the prevalence screening, a rate of 8.3/1,000 overall. The prevalence rate was age-dependent, ranging from 1/1,000 for men age 45 to 49 years to 17/1,000 for men age 65 years and older [2].

Chest radiograph was the most frequent method of detecting prevalence cancers. There were 59 cases detected by radiographs alone, of which 51% were resectable for “cure.” Sputum cytology alone detected 17 cases, of which 94% were considered completely resectable. Fifteen cases were positive by both tests, but only 20% of these were curative resections. Overall resectability was 54%. The survival at 5 years from all causes was approximately 30% among the 91 prevalence patients. This was more than twice the survival observed in a large group of contemporary Mayo Clinic lung cancer cases matched for sex and age [2]. Considering only deaths from lung cancer, the 5 year survival among prevalence cases was nearly 40%. Of the 10,933 men initially screened, only 9,211 also qualified for the randomized controlled clinical trial or incidence study. Additional requirements for the randomized trial included completion of both prevalence screening tests with negative results, a life expectancy of at least 5 years, and respiratory reserve sufficient to permit surgical lobectomy if necessary.

These 9,211 patients were randomized to a screened group, 4,618 men who were asked and reminded to have chest radiographs and 3 day pooled sputum cytologic tests at 4 month intervals for 6 years. The control group of 4,593 patients received only the standard Mayo recommendations for yearly check-ups but no reminders were sent.

A successful randomized trial of screening for lung cancer should initially find more early lung cancers and more early-stage cancers in the screened group than in the control group. Later, during follow-up, the number of lung cancers in the two groups should become equal, as previously undetected cancers in the control group emerge as asymptomatic advanced cancers. Eventually, if treatment for early-stage cancer is more effective, there would be fewer lung cancer deaths in the screened group than in the controls.

From the beginning of the MLP trial, the incidence of lung cancer in the group screened every 4 months outnumbered cases in the control group. By July 1, 1983, all patients had been followed from 1 to 5.5 years, after their 6 years of screening, with median follow-up of 3 years. At that time, 206 lung cancers had been confirmed in the group screened every 4 months, an incidence rate of 5.5/1,000 person-years. There were 160 cases in the control population or 4.3/1,000 person-years of surveillance [3].

About one-fourth of lung cancers in both groups were small cell undifferentiated carcinomas, which are not significantly helped by screening. Only one-third of the cancers in both groups were squamous cell cancers, the type that had been thought most likely to benefit from early surgical treatment. These distributions were much different, and less favourable, than expected when the Early Lung Cancer screening programs began.

In the group screened every 4 months, 90 (44%) of the 206 confirmed cases were detected by the screening tests. In 66 of these 90, only the chest radiograph was abnormal. Eighteen of the 90 cancers were detected by cytologic test alone and six were detected by both screening tests [3].
Of the 116 cases not detected by screening, 73 had symptoms of lung cancer and 43 were discovered by nonstudy chest radiographs obtained for other clinical indications.

Fifteen of the 18 incidence cases detected by cytologic test were resectable. Almost two-thirds of the 115 cancers detected by radiographs were resectable.

Nearly one-third of the lung cancers in the control group were detected by nonstudy chest radiographs and three-fourths of these were resectable. Approximately half of the control population received chest radiographs each year for various clinical indications.

A total of 94 (46%) of the lung cancers in the screened group were resectable compared with 51 (32%) of the 160 in the control group [3]. The 5 year survival in the group screened every 4 months was approximately 35% (lung cancer deaths only). In the control population, it was less than 15%. There were 43 more resectable lung cancers in the close surveillance group screened every 4 months than in controls. However, there were also three more non-resectable cancers in the screened group than in controls (112 compared with 109 in controls). Although approximately half the patients with resectable cancer survived for 5 years, it was rare for those with nonresectable cancers to do so.

The benefits expected from lung cancer screening did not occur. More lung cancers and more early-stage resectable lung cancers were detected in the screened patients than in the controls. But these were not offset by a larger number of advanced unresectable cancers in the control group. The cumulative numbers of unresectable lung cancers were nearly identical in the two groups during the 6 years of initial screening and in later follow-up.

In MLP randomized trial, death rates from all causes were high: 24.8% in the screened group and 24.6% in controls. Ischemic cardiovascular disease was the most common competing death risk. There were 122 lung cancer deaths in the group screened every 4 months and 115 in the control group. The death rate from lung cancer was 3.2/1,000 person-years in the close surveillance screened group and 3.0/1,000 in the control subjects. As with the cumulative numbers of unresectable cancers, the cumulative lung cancer deaths were comparable in the two groups during active screening and in the follow-up period [3].

Results from the other clinical trials at Johns Hopkins and Memorial Sloan-Kettering were basically similar. The randomized controlled trials at Hopkins and Memorial offered all participants annual chest radiographs. Additionally, half had sputum cytologic tests every 4 months. Each studied over 10,000 subjects, for a total of more than 30,000 male smokers age 45 years or older in the three randomized controlled trials. The Memorial and Hopkins studies found that in populations screened by radiographs only, as well as those screened by radiographs and sputum cytology, resectable lung cancers and survival rates were better than results reported from earlier lung cancer screening programs. However, as in the MLP, no significant difference in lung cancer mortality was observed in the two populations [11].

The results of the Cooperative Early Lung Cancer Group randomized controlled trials do not justify recommending large-scale programs of radiologic or cytologic screening for lung cancer. To do so would require benefits to participants by decreasing lung cancer mortality and this benefit did not occur.

These results do not mean that clinical testing of high-risk patients for lung cancer by chest radiographic film or sputum cytology is not useful, as some have claimed. These studies should not be taken as justification for withholding the only potentially useful clinical tests from high-risk patients who come for medical evaluation.

When the NCI randomized controlled trials began, it was generally believed that yearly chest radiographs would not reduce lung cancer mortality. It was also believed that a large proportion of lung cancers would be detected by sputum cytologic tests and the trials were designed on these suppositions. Yet in all three screening programs, the great majority of lung cancers were detected radiographically.

Prevention

The Division of Cancer Prevention and Control announced in 1982 a review and reorganization of priorities in its national cancer prevention program [6, 12]. This strategy begins with epidemiology and basic research, and, in the case of lung cancer, rests firmly on the enormous body of evidence indicating smoking is the causative agent in 80% to 90% of cases.

Subsequent cancer control strategy may be divided into five phases leading to national cancer prevention programs. The first is development of a hypothesis, for example, that smoking prevention or cessation efforts can affect lung cancer incidence and mortality. Phase two is development of methods for intervention and it includes pilot studies. Phase three consists of controlled intervention trials to test the efficacy of a given program in a particular study group, for example, smoking-cessation programs. Phase four consists of defined population studies. An example might be school children of comparable age and sex, either offered a given program of health education or not. Phase five involves applying a given intervention in a large community for demonstration. Costs need to be analysed and efforts made to increase the benefits in relation to the cost invested. When validated in such a sequential strategy, a program is ready to be implemented in broad national programs of public health services.

Tobacco is generally recognized as responsible for 80% to 90% of all lung cancers, and, were it not for cigarette smoking, lung cancer would be low on the list of public health problems. Rather than programs of screening and detection, emphasis has shifted toward more aggressive anti-smoking efforts.

Although many Americans have stopped smoking, an estimated 55 million continue to smoke. It is also estimated that some 85% of smokers would like to stop and over half have tried to stop smoking at least once. For men the lung cancer death rate has increased by 25% in
the past decade, and for women it has almost doubled. Most of this latter trend relates to the increased cigarette consumption among women in the 1950s and 60s. In the US, data for smoking cessation reveal that more adult men are quitting smoking than adult women. The percentage of smokers in the male population declined from an estimated 52.9% in 1964 to 35.2% in 1983. The figures for females are less satisfactory, with the peak rate of 34.1% in 1965, decreasing to 29.1% in 1988 [7, 8].

The age of initiation of the smoking habit is strongly associated with lung cancer risk. Most data suggest the smoking habit is established in the second decade of life. Indications are that in the US the prevalence of smoking among teenagers has stabilized and has begun to decline although for teenage girls it is declining at a slower rate. In 1977, 30% of female high school seniors were smokers and this decreased to 20% in 1984. For male high school seniors, the peak of 28% in 1976 decreased to 16% in 1984. In 1984, 18.7% of all high school seniors were defined as daily smokers; females exceeded the male prevalence rate in the most recent years [13]. These and other data point out the directions for a smoking control program and, thus, a lung cancer control program. Programs of the World Health Organization (WHO), the International Union Against Cancer, and other national programs can be grouped into four major categories: primary prevention programs, smoking cessation programs, legislative efforts, and tobacco product changes.

**Primary prevention programs**

Studies in the United Kingdom by CHARLTON [14] found that most experimentation with cigarettes begins between age 9 and 11 years and regular smoking starts about age 12 or 13 years. She has developed a curriculum for schools that begins at age 9 years and continues until the age of 17 years.

Therapeutic prevention programs should be less difficult and more cost effective than seeking to stop smoking among those already addicted. Educational programs and information can reach large numbers of individuals simultaneously in grade schools with a stable, captive audience. WYNER [15], who established the American Health Foundation, has established a model school curriculum called the "Know Your Body School Health Education Program" (KYB) covering various risk-taking practices, including alcohol, illicit drugs, good nutrition, physical exercise, and sexual hygiene. Smoking prevention is an important part of risk management in this curriculum. He advocates beginning these programs in first grade and continuing yearly throughout the primary grades. However, these prevention efforts can be neutralized by peer and parental smoking role models.

The prevention message is further compromised by clever industry advertising and the widespread availability of cigarettes. Health warnings are often ignored by youths who view themselves as immortal and disease or death only as a remote event that occurs to others.

**Cessation programs**

Data in the literature indicate that the risk of lung cancer decreases after smoking cessation, and 10 to 15 years after stopping the risk decreases to nearly that for nonsmokers [16]. Thus efforts to assist those already habituated to cigarette smoking could have major benefits complementary to the primary prevention efforts. ORLEANS [17] summarized research on smoking-cessation techniques and divided them into five general approaches.

1. The great majority of American ex-smokers, 90% or more, stop on their own. Studies have indicated that 16% to 20% of individuals who make a serious attempt to stop smoking are successful at 1 year [18]. Because of the large numbers involved, efforts to increase the success rate for this group could be a cost-effective strategy. These might include programs helping to boost the initial attempt success rate and efforts to help ex-smokers maintain their abstinence. Wider social support and pressure for quitting can boost the long-term success of stop-smoking attempts. Workplace support and incentives can reach large numbers of individuals and potentially can be more cost effective. Self-help aids for those who have stopped on their own may be particularly helpful. DURREN [19], of the American Health Foundation, noted that people who stopped after a televised smoker’s clinic responded favourably to daily prerecorded telephone messages that provided advice and encouragement. Further research into behaviour modification techniques is desirable to identify improved self-help strategies.

2. Mass media and community programs have been successful in achieving 5% to 10% smoking reduction after 1 year, and these may reach smokers who would not otherwise be motivated to quit [20].

3. Physician advice is another method with low percentage success but potentially cost-effective impact. A British study showed that 5% of smokers were abstinence at 1 year after a brief admonition by their physician and receiving a pamphlet warning of risks and offering suggestions [21]. Given that over 50 million Americans smoke today, even this low yield could potentially convert 2.5 million individuals to safer habits yearly. This type of advice may be especially effective after life-threatening illness is diagnosed. Over 50% of heart attack victims were still not smoking after 1 year in studies reported by BURT et al. in Britain [22] and by WEINBLATT et al. in the US [23].

Patients who have early obstructive airways disease form another group with potentially significant benefit from positive medical advice. There is a need for greater involvement by all physicians and allied health workers in this educational effort.

4. "Quit clinics" represent another popular form of treatment to quit smoking that is available to the American public. Programs are conducted by commercial clinics, noncommercial clinics, and in the health care community. Studies of "Smokenders" clinics showed 70% initial success and 35% to 40% quitting success after 1 year [24]. Their higher response rate may result from the added motivation of paying a substantial fee, as high as $500.00,
Advertising fairly strict regulation in Scandinavia and the countries that had some type of restriction, ranging from cigarette legislation to control smoking.

Labelling requirements. As of 1986, there were 41 countries requiring health warnings on cigarette packages. Many of these are weak, small, impersonal, and relatively ineffective. Warning labels have been required in the US for 20 years, and, since 1985, stronger warnings have been required, which rotate at 3 month intervals on each cigarette package.

Advertising restrictions. More countries have restricted cigarette advertising than have instituted any form of legislation to control smoking. In 1982, there were 42 countries that had some type of restriction, ranging from fairly strict regulation in Scandinavia and the United Kingdom to relatively moderate restriction in the US. Currently, television and radio advertising of cigarettes is prohibited but not print or billboard advertising. Canada recently enacted legislation to also tighten curbs on print advertising and to limit sponsorship of sporting events. The challenge is to eliminate all forms of advertising and thus reinforce the image that smoking is socially unacceptable.

Other regulations include restriction of smoking in public places, and 37 countries have passed legislation limiting public smoking to some degree. In the United States such control is under the jurisdiction of state or local government and this varies widely. The Minnesota Clean Air Act was among the earliest and strictest state laws limiting public smoking. New York City recently enacted ordinances that have been widely publicized. Smoking is now prohibited on all domestic airline flights of less than 2 hours, duration, and one airline, Northwest Orient, has prohibited smoking on all its domestic flights. An increasing number of health organizations and private companies have become smoke free. Since 1987, the Mayo Clinic has prohibited smoking in all buildings and on the grounds as an example for patients and as a commitment to our employees' health. It is difficult to measure the effects of these regulations but they appear to strengthen the effects of public health education, which, in turn, helps to implement legislation.

5. Behavioural approaches incorporate some form of aversive conditioning into programs to teach behavioural self-control skills. The focus is to change attitudes about smoking from positive to negative. Some programs may include smoke as the aversive stimulus, whereas others use positive reinforcement for nonsmoking. Hypnosis and acupuncture may be included in this category, although the mechanisms of action are poorly understood.

Legislative measures

More than 60 countries have some form of government policy to prohibit or restrict smoking. These vary widely in the strength or specificity of laws. ROEMER [25] edited a WHO study summarizing government efforts to combat smoking and most of the following discussion is taken from that source or from the reviews by CULLEN et al. [7, 8].

Taxation. Increased taxation on tobacco and tobacco products has raised prices and decreased consumption. Generally, there is correlation with the level of antismoking activity in a country and the level of taxation. A 10% increase in price appears to cause about a 4% decrease in consumption among adults and an even greater decrease among teenage smokers. An advantage of taxing tobacco is that government revenues overall are increased. An objection is that the impact may be greater for low-income smokers, and taxation may influence total daily consumption, but overall smoking prevalence may be unchanged. Other economic incentives include lower insurance rates, which have become increasingly common in the US insurance industry. Life insurance rates are lowered for nonsmokers and automobile insurance premiums are less, serving to remind smokers of their greater risks. The WHO has urged nations to end agricultural subsidies for tobacco production, something that, as yet, has not occurred in the US. Countries are encouraged to develop economic incentives for production of alternative crops so that economic policies can be brought into accord with public health objectives.

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Tobacco product changes

The most significant trend since the late 1950s has been the shift to low-tar and low-nicotine cigarettes. The mean tar delivery per cigarette has been reduced by roughly 50% over the past 30 years in the US, Canada, Scandinavia, and the United Kingdom, leading to an estimated 20% decrease in lung cancer risk. This approach may be politically practical but it has serious limitations for a public health strategy. The reduction in risk is minimal compared with cessation. Product change does not alter the appeal to youth, which is critical for childhood smoking initiation. The risks for heart disease, obstructive lung disease, and other cancers are not necessarily reduced by using low-tar cigarettes.

Summary

In 1984, the NCI in the US adopted, as a national goal, reduction of cancer mortality by 50% by the year 2000. It is hoped that this can be accomplished with 25% gained from a broad national detection and treatment effort, and 25% mortality reduction through primary prevention.

The NCI Smoking Tobacco and Cancer Program (STCP) has set three specific goals for the year 2000: to reduce the percentage of adults who smoke from 34% (1980) to 15% or less, to reduce the percentage of youths age 12 to 18 years who smoke to 3% or less and to reduce the percentage of high school seniors who smoke to 3% or less.
The strategy to achieve this goal is an intensive intervention program applying biomedical and behavioural research. The approaches that will receive top priority in the STCP are: mass media advertising to encourage a social climate for smoking abstinence; school-based intervention to prevent initiation of tobacco use among children and adolescents; physician and dentist intervention to supply health information and encouragement; self-help strategies that most current smokers say they would prefer. With these intensified efforts in education and behaviour modification, the expectation is for significant reduction in lung cancer incidence and mortality by the end of this century.

References


RÉSUMÉ: Le cancer bronchique est un problème majeur de santé publique aux États-Unis et la première cause de mort d’origine cancéreuse à la fois chez les hommes et chez les femmes. Au début des années 1970, l’Institut National du Cancer (NCI) a soutenu des essais cliniques multicentriques pour apprécier les effets du dépistage par cytologie de l’expectoration et examens radiographiques du thorax en série sur la mortalité par cancer du poumon chez des fumeurs à haut risque de sexe masculin. Quoique l’on ait détecté un plus grand nombre de cancers, que l’on ait réduit un plus grand nombre de cancers précoces du stade I, et que les taux de survie à 5 ans soient améliorés dans les populations déplacées plus que chez les contrôles sans dépistage, l’on a noté des nombres quasi égaux de cancers avancés, et les taux de mortalité ne s’avèrent pas significativement différents. Dès lors, le dépistage de masse pour la détection du cancer pulmonaire précocé n’a pas été poursuivi comme politique de santé publique aux États-Unis. Dans les années 1980, l’attention s’est déplacée vers les efforts de prévention du cancer du poumon par des programmes éducatifs visant à la prévention et à la cessation du tabagisme. En 1984, l’Institut National du Cancer a adopté comme objectif national la réduction de la mortalité par cancer du poumon de 50% d’ici l’an 2000. La stratégie choisie pour arriver à ce résultat est un programme intensif de changement de comportement visant; à encourager un climat social pour l’abstinence tabagique; à prévenir le début de l’habitude tabagique chez les enfants et chez les adolescents; à fournir du matériel d’éducation et d’encouragement au travers des professionnels de la santé et de programmes basés sur la communauté.