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Commonplace to condemned: The discovery that tobacco kills, and how Richard Doll shaped modern smoking cessation practices

Dr Richard Doll's unpopular conclusion in 1950 that smoking causes lung cancer and heart disease led to a dramatic shift in social practices and medical interventions.

ABSTRACT: Sixty years ago, smoking was a favorite pastime. Few suspected that this seemingly innocuous habit was responsible for the skyrocketing incidence of lung cancer in the UK following the Second World War. Dr Richard Doll pioneered research that demonstrated the link between smoking and lung cancer and showed its detrimental effect on the cardiovascular system. Today the health risks of smoking are well known, yet millions of people die prematurely each year due to the damaging effects of this habit. Smoking cessation can lead to dramatic improvements in health, so it is important for physicians to understand the factors that prevent patients from quitting and the resources available. The greatest success rates for smoking cessation result from combining medical and psychosocial support.

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In the early 1950s 80% of middle-aged men in the UK smoked and only 0.5% said they had never touched a cigarette. The Second World War was over and it was a time of social progress and general merriment. Nevertheless, an ominous threat loomed on the horizon. The incidence of lung cancer in young men skyrocketed after the war and rapidly overtook tuberculosis as the major cause of death in the UK.[1] This alarming development resulted in considerable investment by the Medical Research Council (MRC) to determine the epidemiology of the disease. Today, less than 30% of men in the UK smoke and the knowledge that smoking causes lung cancer and cardiovascular disease is well established, all because of the work of one scientific pioneer who dared to threaten social convention with statistics.[2]

Dr Richard Doll

Sir (William) Richard Shaboe Doll was born in 1912 in Hampton, Middlesex. His father Henry was a physician who pressured his son to pursue a medical career because it would provide financial stability. Doll, however, was more interested in the elegance of numbers and enrolled in mathematics at Cambridge. After enjoying a lively dinner at Trinity College, which included several pints of his fellows' home-brewed beer, Doll failed his math exam the next morning. He was

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Sir Richard Doll, 1912–2005.

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so irritated with himself that he declined the university's offer to let him rewrite the test and instead exclaimed, "Oh, damn it, I won't do mathematics, I'll do medicine as you want, Father."[3] No one could have guessed that a career change instigated by a few too many drinks would result in the prevention of thousands of premature deaths worldwide and the evolution of scientific medical research.

Doll's research, activism, and careful statistical science established the standard for evidence-based modern medicine.

Doll graduated from St. Thomas' Hospital Medical School in London in 1937. During his education and early career, he delivered babies in slums around the city and became a political revolutionary, rallying for social reforms that would grant patients of all economic backgrounds access to medical care.[1] Doll served in the Royal Army Medical Corps during the Second World War, but was so disgusted by the pompousness of the senior staff that he turned away from clinical practice and back to his passion for numbers to begin a career in epidemiology. In 1947 the MRC offered Doll a research position with Dr Austin Bradford Hill to investigate the rising rates of lung cancer in the UK.[3]

Doll's research, activism, and careful statistical science established the standard for evidence-based modern medicine. Because of his work on the health hazards associated with smoking, Britain experienced the world's greatest decrease in premature death, with the rate of men dying before age 70 dropping from 20% in 1970 to 5% in 2005, the year of Doll's own death. Doll's accomplishments include over 400 publications and 20 major scientific awards, including honorary degrees from 13 universities. In 1971 he was knighted by Queen Elizabeth II for his great service to humanity.

Doll's unpopular discovery

In 1950 Doll began interviewing patients with lung, stomach, colon, or rectal cancer from 20 London hospitals in order to pinpoint an underlying environmental or social factor that would explain the dramatic rise in lung cancer. Initially, he believed that tar from road construction was to blame, since it was known to release many carcinogens into the air.[2] A study of more than 700 lung cancer patients younger than 75 and the same number of age- and gender-matched controls revealed the common link: smoking. This initial study demonstrated that smoking was strongly related to lung cancer, but not to other lung diseases nor to cancers of other organs. Doll concluded that "smoking is a factor, and an important factor, in the production of carcinoma of the lung."[4] He himself had been an avid smoker for 19 years, but quit in 1949 as he began to realize its deleterious effects on his health.

Intense resistance to the idea that a pastime as enjoyable as smoking was responsible for lung cancer spurred Doll to begin another massive study in 1951. This time he targeted doctors because they were likely to complete the study questionnaire accurately and were relatively easy to follow through the UK's registry of physicians. Questionnaires were completed by over 40 000 doctors, of whom 87% were smokers, and 789 deaths were analyzed. Again, the results published in 1956 showed that increased mortality from lung cancer and coronary thrombosis was directly related to the amount smoked.[5]

Doll sent follow-up questionnaires to the surviving doctors and published the results in 1957, 1966, 1971, 1978, 1991, and 2001. He undertook a final 50-year assessment in 2004. Over 30 000 doctors were retained in the study for the full 50 years, allowing for the analysis of more than 25 000 deaths. The conclusion of the final study showed that over half of the deaths were due to lung cancer, chronic obstructive pulmonary disease (COPD), or ischemic heart disease related to smoking, and that long-term smokers lived an average of 10 years less than nonsmokers. Doll was also able to determine that smoking cessation at 50 years of age cut the risk of premature death in half, while cessation at 30 nearly eliminated the risk altogether.[6]

Health risks associated with smoking

The health risks associated with smoking are now well understood and documented, thanks to Doll's pioneering research. The major cardiovascular and respiratory considerations are summarized by Godtfredsen and Prescott[7] and outlined below:

- Smoking more than doubles the risk of cardiovascular disease (including myocardial infarct, stroke, peripheral arterial disease, abdominal aortic aneurysm, and chronic heart failure); there is a dose-response relationship between the inherent risk and the amount of tobacco smoked.

- Incidence of myocardial infarct under age 35 is highly associated with heavy smoking, and continued smoking is the greatest predictor of a repeat heart attack.
- Although Doll enraged antismoking lobby groups by denying the danger of secondhand smoke, secondhand smoke is now known to be a considerable health concern. When Europe and North America banned smoking in public locations, this decreased the incidence of myocardial infarcts by 17%.
- More than 50% of chronic heart failure is due to ischemic heart disease associated with smoking.
- Smoking increases the risk of lung cancer, COPD, some interstitial lung diseases, and upper respiratory tract infections. COPD patients are also more susceptible to community-acquired pneumonia.

Remarkably, the cardiovascular risk profile is almost completely reversible if the individual stops smoking before the age of 35, and benefits can be seen throughout the cardiovascular system. Smoking cessation prevents coronary heart disease, reduces stroke risk, and halts the progression of peripheral arterial disease. Ex-smokers and nonsmokers with abdominal aortic aneurysms have identical risk profiles for death and rupture, but the risk is much higher in those who continue smoking. Lung function also shows improvement with smoking cessation, even in people who have already developed symptoms. The forced expiratory volume in 1 second (FEV_1) is the same in individuals who quit smoking before age 30 as it is in nonsmokers; however, smoking reduction does not show this benefit.[7,8] Smoking cessation is so beneficial to health that physicians should know how to assist their patients by diagnosing tobacco addiction and supporting those ready to quit a dangerous habit.

How to diagnose tobacco addiction

Most patients are willing to reveal their smoking status; however, statistics show that only 8% of smokers quit without help. Therefore, the challenge for physicians lies in recognizing when patients are ready to receive help and knowing how to move recalcitrant smokers to the realization that they need help.[9]

Diagnosis of nicotine dependence can be made using simple tools, such as the abbreviated Fagerström test (**Table 1**). These tools enable the physician to determine the degree of addiction, but do not indicate whether the patient is interested in addressing it. An understanding of the psychological stages through which smoking patients progress before being willing to quit (**Table 2**) allows the doctor to identify where patients are in their thinking about cessation. The physician may then use motivational interviewing techniques to move the patient through these stages to a realization of the need for change that will result in action. This often involves discussing the impact that smoking is having on the patient's life and on loved ones, as well as the short- and long-term health risks to which they are exposing themselves. Every patient has a unique story; the physician should consider the circumstances surrounding the patient's choice to begin smoking, the social and physiological factors compelling them to persist in the habit, and the fear and shame associated with their inability to quit.

How to facilitate smoking cessation

Physicians can facilitate smoking cessation with the help of the Five A's (**Table 3**) recommended by the US Public Health Service and described in more detail by Okuyemi and colleagues.[10] Physicians should know that even when a patient is motivated to stop smoking, and is treated appropriately, many health effects associated with smoking cessation, such as weight gain, can act as deterrents to

Table 1. Fagerström test for nicotine dependence.[9]

- How soon after waking do you smoke your first cigarette?
  - ☐ Longer than 60 minutes (0 points)
  - ☐ 31 to 60 minutes (1 point)
  - ☐ 5 to 30 minutes (2 points)
  - ☐ Less than 5 minutes (3 points)
- How many cigarettes do you smoke each day?
  - ☐ 10 or fewer (0 points)
  - ☐ 11 to 20 (1 point)
  - ☐ 21 to 30 (2 points)
  - ☐ More than 30 (3 points)

Scoring key for nicotine dependence:
5–6 points = heavy
3–4 points = moderate
0–2 points = light

Table 2. Stages of readiness to change.[9]

1	**Precontemplation**	Not planning to quit within the next 6 months
2	**Contemplation**	Considering quitting within the next 6 months
3	**Preparation**	Planning to quit within the next 30 days
4	**Action**	Has successfully quit for less than 6 months
5	**Maintenance**	Has successfully quit for at least 6 months

Table 3. Five A's model for facilitating smoking cessation.[10]

Ask about tobacco use during every office visit
Advise all smokers to quit
Assess the patient's willingness to quit
Assist the patient in his or her attempt to quit
Arrange follow-up contact

Table 4. Negative health effects of smoking cessation.[8]

Effect	What patient needs to know
Weight gain (with an average increase in BMI of about 1kg/m²) can be both a deterrent to abstain from and an excuse to resume smoking.	The increased risk of cardiovascular disease associated with a higher BMI does not counterbalance the much greater risks of continued smoking.
Increased incidence of hypertension is greater in people who stop smoking (OR=1.8) than in smokers (OR=1.3) due to unknown mechanisms. Blood pressure (BP) may rise independent of weight change.	The cardiovascular benefits of smoking cessation (decreased arterial stiffness and improved lipid profile) dramatically outweigh the risks of increased BP.
Increased sputum production and respiratory tract infections are seen following an attempt to stop smoking, partially due to decreased levels of secretory immunoglobulin A.	Sputum production and infections decrease over time if the patient continues to abstain. Those who continue smoking have a substantially increased risk of bacterial pneumonia, influenza, and tuberculosis.
Constipation affects 17% of those who stop smoking and may be severe in 9%.	Constipation peaks at 2 weeks after smoking cessation and usually abates at around 4 weeks. Symptoms can be treated with diet, fibre, water, and exercise.
Mouth ulcers may occur in 40% of patients within 2 weeks after smoking cessation and may be severe in 8% of patients.	Ulcers typically resolve within 4 weeks in the majority of patients, and are not a side effect of smoking cessation medications.
Altered drug metabolism by cytochrome P450 1A2 (CYP1A2) is associated with smoking.	Following smoking cessation, there may be a need for dose changes of analgesics, anticoagulants, antidepressants, muscle relaxants, anticonvulsants, antipsychotics, cancer treatments, antiemetics, antiarrhythmic agents, beta blockers, and other medications.

quitting. The key to overcoming these deterrents is to prepare, reassure, and encourage patients to persist in making this positive change for their health and to manage their symptoms. Some of the negative effects of smoking cessation and what patients need to know about them are summarized in **Table 4**.

Numerous pharmacological interventions are available for patients who wish to stop smoking; however, the greatest success rates are achieved by combining medical and psychosocial support. Up to 35% of smokers are able to abstain from tobacco for 1 year when a combination of nicotine replacement therapy (NRT), bupropion, and behavioral modification techniques are utilized.[9]

Medical support

Nicotine withdrawal in addicted individuals is characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbance, impaired concen-

Table 5. Nicotine replacement therapies.

Therapy	Mechanism and dose	Risks
Patch	Provides a constant dose of nicotine through the skin, peaking at 6–12 hours after application. Most common side effect is local skin irritation, which is more common with the 24-hour patch than the 16-hour patch. This can be reduced by changing the locations of the patch. Sleep disturbance is more common with the 24-hour patch and with increased doses, but there is no statistical difference in quit rates between the 24- and 16-hour patches.	Health risks, such as platelet disturbances, are not as serious as the risks associated with continued smoking. Patients who continue to smoke while using the patch may experience nicotine toxicity.
Gum	Available in 2-mg and 4-mg doses, with a higher dose recommended for patients who smoke more than 25 cigarettes per day. One piece of gum is chewed every 1–2 hours for the first 6 weeks, 2–4 hours for the next 3 weeks, and 4–8 hours for the last 3 weeks.	Gum is considered a Category C drug during pregnancy, while all other forms of NRT are Category D. Use cautiously after an acute cardiovascular event, knowing that the benefits typically outweigh the risks.
Lozenge	Available in 2-mg and 4-mg doses. Those who smoke within 30 minutes of waking up should use the higher dose. Utilization is the same as for gum.	
Inhaler	Each cartridge contains 4 mg of nicotine. The patient should use 6–16 cartridges per day for 12 weeks and then slowly taper the usage over the next 6–12 weeks.	
Nasal spray	Each spray contains 0.5 mg of nicotine, and this method of administration provides the fastest dose. The patient should use one or two sprays in each nostril every hour for 3–6 months and then slowly taper the usage over the next 4–6 weeks.	

tration, increased appetite, and weight gain.[9] Nicotine replacement therapy mitigates these symptoms during early abstinence, and therefore doubles the cessation rate.[9-11] In general, NRT has few side effects, with most complaints being specific to the method of administration (i.e., itchiness at the patch site, jaw pain with gum, mouth and throat irritation with the inhaler and lozenge, and a runny nose with the inhaler). The various types of nicotine replacement therapies are summarized in **Table 5**.

Bupropion (Zyban) is recommended for smoking cessation along with NRT. The rate of smoking cessation after 1 year of treatment with this drug, together with minimal or moderate counseling, ranges from 23% to 33%. Bupropion works by inhibiting norepinephrine, serotonin, and dopamine reuptake, and is weakly antagonistic to nicotinic receptors. It can be used for smoking cessation and reduction.[9,10]

Clonidine (Catapres) and nortriptyline (Pamelor) are second-line agents,[9,10] neither of which was included in a recent meta-analysis published in the *Canadian Medical Association Journal*.[12] Clonidine is an alpha-2 receptor agonist that is used primarily as an antihypertensive agent. It has been shown to effectively decrease the withdrawal side effects of multiple drugs, including nicotine.[13] The side effects of clonidine include postural hypotension, rebound hypertension, dry mouth, drowsiness, dizziness, and sedation. Nortriptyline is a noradrenergic tricyclic antidepressant that significantly reduces most withdrawal symptoms. Its side effects include dry mouth, dysgeusia, gastrointestinal upset, drowsiness, sleep disturbance, possible cardiac dysrhythmias, and toxicity if taken in excessive amounts. Most studies have examined its effectiveness in combination with intense counseling in depressed patients.[13]

Varenicline (Champix) is considered the most effective smoking cessation aid and works by facilitating dopamine release and maintaining partial stimulation of the alpha-4 beta-2 nicotinic acetylcholine receptors.[12,14] In a study of patients with stable cardiovascular disease, varenicline use was shown to be effective and resulted in a nonsignificant decrease in death from all causes. The study suggested that varenicline is safe, but was not powerful enough to conclusively establish the safety of the drug.[14] A further meta-analysis demonstrated an absolute risk increase of 0.24% for a major cardiovascular event in those using varenicline versus placebo.[15] However, given varenicline's ability to more than double the rate of smoking cessation (OR 2.41; 95% CI, 1.91–3.12) the benefits of this medication appear to outweigh the associated risks.[12,14]

Psychosocial support

Repeated reinforcement of the need to stop smoking from nonthreatening sources is associated with a high compliance rate.[16] Physicians should ask about smoking at every visit, follow up with the patient, evaluate relapse triggers, and encourage abstinence.[9,10] However, this burden does not need to fall on the physician alone. Many jurisdictions provide smoking counselors, group therapy, and smokers' help lines. There are also numerous online resources for patients in British Columbia who wish to stop smoking (**Table 6**), including a workbook called "On the Road to Quitting," which reminds patients of the health, social, and financial benefits of quitting as it guides them through the cessation process. This workbook is available online, and anyone can order up to 10 English and 10 French print copies for free. It can also be provided in large print, diskette, audiocassette, and braille form.[15]

Table 6. Smoking cessation resources for BC patients.

- Smokers Help Line: 1 877 455-2233
- "On the Road to Quitting" workbook www.hc-sc.gc.ca/hc-ps/pubs/tobac-tabac/orq-svr/index-eng.php
- Resources for BC adults www.quitnow.ca
- Resources for BC young adults (ages 19–29) www.quittersunite.com
- Resources for Canadian teens www.quit4life.com

Teaching patients behavior modification techniques can also make the difference between a successful attempt to stop smoking and a series of frustrating relapses. Some effective strategies include the removal of triggers associated with smoking from the patient's surroundings. Eliminating cigarettes, lighters, matches, and ashtrays from the home makes it more difficult for the patient to indulge. Choosing to go where smoking is not permitted may also be helpful. For example, rather than going to the patio where co-workers typically smoke and socialize during breaks, the patient could choose to visit a nearby coffee shop where smoking is prohibited. At home, hobbies such as knitting or model building can keep the patient's hands occupied. Another helpful strategy can be habitual replacement. When the urge to smoke is felt, the patient can turn to a healthier habit, such as chewing gum or eating carrot sticks. Habitual replacement allows the patient to handle an object in a similar manner to a cigarette without the deleterious health risks.

Despite all these techniques and strategies, the most critical psychosocial factor in successful smoking cessation is support from family and close friends. The physician is advised to meet with the patient and his or her

partner to talk about the importance of support and accountability. If the partner is also a smoker, the risk of relapse is extremely high and the partner should be strongly encouraged to commit to a program of abstinence as well.

Reduction vs cessation

The benefits of smoking reduction have been debated in the medical literature.[9,10,16] In general, the health benefits noted in patients who stop smoking altogether are not found in patients who simply reduce their nicotine consumption. However, many of these risks are dose-dependent, so reduction in the amount smoked could decrease the patient's probability of a significant cardiovascular event. One study suggests that smoking reduction is critical for patients who want to stop smoking[16] because the combination of smoking and NRT can maintain the patient's nicotine dose while reducing the amount of time the patient engages in the activity. This gives patients a sense of control over their smoking patterns and helps them change their behaviors. Gradual accomplishments further motivate the patient to stop smoking, and reduce the severity of withdrawal symptoms. Physicians ought to support patients who are motivated to reduce their nicotine intake, and provide information and encouragement to move them toward complete abstinence.

Summary

Millions of people die prematurely each year as a result of smoking. Fortunately, fewer smoking-related deaths occur today than in the past because of the pioneering work of Dr Richard Doll, who established the standard for evidence-based modern medicine and demonstrated the link between smoking and lung cancer. Doll also confirmed the detrimental effect of tobacco use on the cardiovascular system. Physicians can help their patients by diagnosing tobacco addiction and recommending the combined use of nicotine replacement therapy, a medication such as bupropion or varenicline, and psychosocial support.

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Competing interests

None declared.

References

1. Wood J. Life of a revolutionary. University of Oxford website. Last updated 13 May 2010. www.ox.ac.uk/media/science_blog/091111.html.
2. Sir Richard Doll: A life's research. BBC News. Last updated 22 June 2004. http://news.bbc.co.uk/2/hi/health/3826939.stm.
3. McKie R. The Observer profile: Richard Doll. Topic of Cancer. The Guardian 7 July 2002. www.guardian.co.uk/education/2002/jul/07/research.highereducation.
4. Doll R, Hill AB. Smoking and carcinoma of the lung. Preliminary Report. 1950. Bull World Health Organ 1999;77:84-93.
5. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: A preliminary report. 1954. BMJ 2004;328:1529-1533.
6. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519-1528.
7. Godtfredsen NS, Prescott E. Benefits of smoking cessation with focus on cardiovascular and respiratory comorbidities. Clin Respir J 2011;5:187-194.
8. Gratziou C. Respiratory, cardiovascular and other physiological consequences of smoking cessation. Curr Med Res Opin 2009;25:535-545.
9. Mallin R. Smoking cessation: Integration of behavioral and drug therapies. Am Fam Physician 2002;65:1107-1114.
10. Okuyemi KS, Nollen NL, Ahluwalia JS. Interventions to facilitate smoking cessation. Am Fam Physician 2006;74:262-271.
11. Nides M. Update on pharmacologic options for smoking cessation treatment. Am J Med 2008;121(4 suppl 1):S20-31.
12. Eisenberg MJ, Filion KB, Yavin D, et al. Pharmacotherapies for smoking cessation: A meta-analysis of randomized controlled trials. CMAJ 2008;179:135-144.
13. Frishman WH, Mitta W, Kupersmith A, et al. Nicotine and non-nicotine smoking cessation pharmacotherapies. Cardiol Rev 2006;14:57-73.
14. Rigotti NA, Pipe AL, Benowitz NL, et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: A randomized trial. Circulation 2010;121:221-229.
15. On the road to quitting: Guide to becoming a non-smoker. Ottawa: Health Canada; 2007. www.hc-sc.gc.ca/hc-ps/alt_formats/pdf/pubs/tobac-tabac/orq-svr/cbns-gdnf-eng.pdf.
16. Le Houezec J, Säwe U. Smoking reduction and temporary abstinence: New approaches for smoking cessation. J Mal Vasc 2003;28:293-300. BCMJ