

## Commentary

# A long-term view of harm reduction

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**The concept of harm reduction is controversial, as it brings to mind the failures, public misconceptions, and undermining of prevention associated with the low-tar cigarette campaign. Modern cigarettes are, however, unnecessarily carcinogenic and toxic, a situation that could be improved by sensible and serious regulation of the contents of tobacco smoke. The risks potentially associated with reducing levels of known toxicants in cigarettes are tiny in comparison with the acceptance of the status quo, which is disastrous. Failure to act in these circumstances is negligence.**

### Introduction

Harm reduction, which can be defined as attempts to reduce exposure in persisting tobacco users—either by reducing amounts of toxins/carcinogens in smoke or reducing amounts of smoke inhaled—is controversial, whereas the two primary approaches to reducing tobacco-related mortality and morbidity, cessation and prevention of initiation, are widely considered crucial. Although it is obvious that improving cessation rates will give more immediate mortality benefits than prevention of initiation, there are no excuses or valid reasons for not pursuing both objectives as seriously as possible. Further, there are no consequential downsides associated with either of these policy objectives. Harm reduction, however, not only carries risks; it has a checkered history that includes, arguably, more evidence of harm than good. Light cigarettes derailed cessation and undermined prevention (Stratton, Shetty, Wallace, & Bondurant, 2001), and oral tobacco use was taken up by young athletes who had been considered to be at low risk for

any type of tobacco use (Connolly et al., 1986). It is timely, in 2004 (when relevant legislation is possible both in the United States and Europe), to take a long view of the issue and to consider whether tobacco should be treated and regulated as pharmaceutical drug delivery devices are.

### The past

The concept of harm reduction, as applied to tobacco use, has been with us since the introduction of the filter cigarette, which appears to have been developed originally as a marketing ploy in the early 20th century, when various cigarette modifications such as filters, and additives such as throat-soothing menthol, were introduced to reduce concerns about the harmfulness of smoking (Stratton et al., 2001). However, it gained respectability during the sixties when the idea of the low-tar cigarette took off, with encouragement by the public health community (U.S. Department of Health and Human Services [USDHHS], 1981).

The logic behind the idea was solid in the context of the times. Three observations were persuasive:

- There was a dose response between cigarettes smoked and disease outcomes (Doll & Hill, 1950; Wynder & Graham, 1950).
- There was reversal of risk when smokers stopped smoking (Doll & Hill, 1950).

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- There was a dose response between the amount of tar (particulate matter) painted on mouse skin and the tumor response (Wynder, Graham, & Croninger, 1953).

It therefore seemed logical that reducing the number of particles should reduce the dose and hence the disease result. This reasoning was not as simplistic as it may seem in retrospect, since the possible decline in (quantitative) tar was potentially (and actually, as it turned out) substantial. What was not foreseen was that the tobacco industry response would be to modify the design of the cigarette to yield lower values when tested by smoking machines, according to the method of the Federal Trade Commission (FTC) and International Standards Organization (ISO), while enabling cigarette smokers to easily inhale the full range of nicotine dosages required by their bodies to avoid withdrawal and sustain addiction (USDHHS, 2001). A second response was to change the qualitative nature of tar in ways that defeated many of the harm reduction objectives anticipated in the 1960s (Hoffmann, Djordjevic, & Hoffmann, 1997).

The medium-term effect on mortality appeared, as late as 1987, to be beneficial, when the International Agency for Research on Cancer (IARC) reviewed seven studies and stated that “the low tar cigarette appears to reduce the risk for lung cancer” (International Agency for Research on Cancer, 1986). Two key studies were particularly influential: Hammond, Garfinkel, Seidman, and Lew (1976) and Wynder and Stellman (1979). Other studies published later were consistent with this conclusion (Tang et al., 1995). During the 1980s, mortality from lung cancer declined in a number of countries, attributed to both reduction in smoking prevalence and quantitative tar yields (Peto, 1986). Certainly, the reduction of mortality, especially among young males in the United Kingdom, is consistent with this view.

The lung cancer mortality in the United States has been extensively analyzed (USDHHS, 2001), leading to the most recent conclusion that “epidemiological and other scientific evidence, including patterns of mortality from smoking-caused diseases, does not indicate a benefit to public health from changes in cigarette design and manufacturing over the last fifty years (USDHHS, 2001, p. 10). It is possible to argue about the exact effects on global mortality, but it is also possible to conclude that both are less than expected and less than they could have been.

The lack of evidence of significant mortality benefit is only one of the unforeseen effects of the tar reduction program. Others include:

- The occurrence of great variation, and some increases, in tobacco-specific nitrosamines (TSNAs) often associated with increases in nitrate content; and curing practices (Fischer, Spiegelhalter, & Preussmann, 1990; Gray et al., 2000; Hoffmann & Hoffmann, 1997). Over
- a similar time period, an important reduction occurred in polyaromatic hydrocarbons, specifically benz(a)pyrene (BaP), which correlates with tar, along with considerable variation in other carcinogens and toxins (Gray & Boyle, 2000).
- The impressive change in lung cancer histology in many countries, including reports of a relative decline in squamous cell carcinoma and a relative increase in adenocarcinoma, which are sometimes absolute as well as relative (Beard, Anneges, Woolner, & Kurkland, 1985; Cox & Yesner 1979; Cutler & Young, 1975; Devesa, Shaw, & Blot, 1991; El-Torky, El-Zeky, & Hall, 1990; Johnson, 1988; Thun & Heath, 1997; Thun et al., 1997; Vincent et al., 1977; Wu et al., 1986; Wynder & Muscat, 1995; Young, Percy, & Asire, 1981; Zheng et al., 1993). Since BaP is a powerful squamocarcinogen and, among the TSNAs, 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a powerful adenocarcinogen (Hecht, 1999), it seems very likely that these relationships are causal (Gray & Boyle, 2000; Hoffmann et al., 1997). The decline in squamous carcinoma certainly is related to decline in prevalence as well as changes in chemistry, but the increase in adenocarcinoma can only be related to changes in composition of the smoke and the way the cigarette is smoked.
- The cigarette became more elastic, i.e. it facilitated compensatory smoking, primarily as a result of filter ventilation and other design changes (Kozlowski, O'Connor, & Sweeney, 2001). Thus, total puff volumes increased, as did exposure to the peripheral part of the lungs.
- The cigarette became more efficiently addictive through use of ammonia technology, other additives, and clever design developments (Royal College of Physicians, 2000).
- The cigarette became “smoother” and easier to smoke and, presumably, to learn to smoke (Wayne & Connolly, 2002).
- The public became subject to serious misconceptions about the risks of low-yield cigarettes, and the summarized evidence strongly suggests that this had the effect of reducing quitting (Weinstein, 2001).

### The present

The result of the 50-year historical developments described above is the status quo of today, which can only be described as disastrous. Today's cigarette is highly addictive, misleadingly labeled, facilitates compensation, is easy to learn to smoke, and delivers unnecessarily high levels of carcinogens and toxins. Its manufacture is not subject to meaningful regulation of its toxicant delivery.

It is unlikely that the history would be the same if tobacco products had been subject to regulation of the sort that applies to pharmaceutical products, but they have not and are not. The European Union (EU) is in the process of introducing regulation of additives and has forbidden “health” (or disease-related) claims such as “light” and “mild,” but carcinogen dose remains uncontrolled and unknown to the consumer. Legislation under consideration in the U.S. Congress might hand regulatory powers in that country to the U.S. Food and Drug Administration (FDA), but the strength of such powers is yet to be defined. Articles of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) require regulation of tobacco product constituents and labeling but have yet to be implemented. Thus, in no country is there comprehensive regulation of the chemical nature of tobacco products, despite substantial legislation covering the way in which products are advertised and sold.

Therefore, questions must be asked: Is harm reduction feasible? If so, is it ethical and sensible to proceed down what is now a well-worn path? What should the policy of the future be?

#### *Feasibility of reducing product toxicity*

Since harm reduction implies a substantial reduction in the dose of carcinogens and toxins in cigarette smoke, current industry manufacturing practices answer this question. Wide variation exists in the toxin levels emitted by products presently on the market, and this variation provides potential targets that all products might be expected to achieve. Proper initial targets are not difficult to set. However, separate and more complex issues must be considered when dealing with nicotine (Bates et al., 1999; Gray & Boyle, 2003; Henningfield & Slade, 1998), and no consensus has yet emerged (Gray & Boyle, 2003; Henningfield et al., 1998).

#### *Carcinogens and toxins (toxicants)*

Although data are few, enough findings exist to describe what is currently being done, and hence what is possible. What follows refers to two major carcinogens (Hecht, 1999) and serves as an example.

**Table 1.** Levels of benz(a)pyrene (BaP) and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in two Australian cigarette brands.

Brand	BaP, Int., ng	NNK, Int., ng
Peter Jackson Ultra Mild	14.4	42
Winfield-KS	17	76.5

Int., intense measuring system.

Table 1 shows data extracted from the Australian Department of Health and Ageing Website (Australian Department of Health and Ageing, 2001), which gives a sample of emissions of 15 popular brands tested by the Canadian “intense” measuring system (puff volume 55 ml, every 30 s, all ventilation holes in filter taped over). The lowest and highest brands are selected for comparison.

In comparison, Table 2 shows the lowest and highest from a sample of 26 U.S. brands tested by the Massachusetts measuring system (puff volume 45 ml, every 30 s, 50% of ventilation holes taped over) (Gray & Boyle, 2002), which would be expected to show a relatively lower amount of the substance being tested.

We may conclude from the Australian data that a cigarette delivering 14.4 ng of BaP and 42 ng of NNK (Canadian measurement system) can be made and marketed. The comparison with the U.S. brands is somewhat difficult, since the Massachusetts system delivers significantly lower total puff volumes, and hence shows relatively lower carcinogen yields (which emphasizes the need for an updated measuring standard), but the data are included to demonstrate that brands differ greatly in levels of these smoke carcinogens, including one that is relatively low.

Furthermore, these data demonstrate that it is technically and commercially feasible to make cigarettes with substantially lower levels of BaP and NNK, compared with those that are typical in commercially available cigarettes. In principle, this reductionist approach could be extended to determine the range of levels of lung toxicants such as acrolein, and cardiovascular toxicants such as carbon monoxide, to establish technically feasible levels for the setting of standards.

The tobacco industry might object on the grounds that cigarette smoke is a complex mixture, and reducing toxicants might not be easy. On this point, implementation would require oversight by appropriate regulatory authorities to ensure that the industry is doing all that it can to achieve target levels. The industry might also claim that there is little evidence that reducing specific toxicants would reduce the harmfulness of the products. On this point, we would agree, and would assert that that would be the basis for precluding harm reduction claims on the basis of these modifications. Nonetheless, such efforts

**Table 2.** Levels of benz(a)pyrene (BaP) and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in two U.S. cigarette brands.

Brand	BaP, Mass., ng	NNK, Mass., ng
Merit	5.1	54.2
Camel	34.7	220

Mass., Massachusetts measuring system.

would seem to be important incremental steps in a process that could lead eventually to cigarettes with substantially reduced overall harmful potential.

#### *Feasibility of reducing harm at population levels*

Because the health effects of a product can be determined as much by how a product is used as by how the product is made, simply reducing toxicant emission of products would not be a sufficient basis for making or implying harm reduction claims (Stratton et al., 2001). Nonetheless, the intent of such product modification would be to reduce the public health damage related to smoking, and thus, product modification would ideally be supported by communications intended to support patterns of product use that did not undermine prevention and cessation, and that did not subvert the intent of the product modification for individuals (e.g., smoking more of the presumed safer products). It would also be essential to develop appropriate surveillance so that population effects could be tracked to enable corrective actions to minimize undesirable effects and maximize the desirable outcomes.

#### *Feasibility of reducing harm at a personal level*

Although we have focused on reduction of toxicants and cigarette design, it is important to note that smoking reduction, aided or not by nicotine replacement therapy (Bolliger et al., 2000), has a potential role—as do any other dose reduction maneuvers, such as reduced inhalation, change to less toxic forms of tobacco—in the everyday life of many smokers, particularly those with smoking-associated disease. The potential for harm reduction at the individual level is suggested also by analyses of populations at especially high risk, such as pregnant women and people with cardiovascular disease (Stratton et al., 2001; Windsor, Oncken, Henningfield, Hartmann, & Edwards, 2000).

#### *Ethics and common sense*

We propose that it is unethical to accept the status quo, where the worst nicotine delivery system is ubiquitously available, affordable, widely advertised in such global forums as Formula One, and unregulated. Only in a regulated environment can the policies discussed here be applied. The lesson of history is that common sense may not prevail, since not only is regulation needed, but good regulation is absolutely essential.

#### **The future**

Given the existing legislation in the European Union, laying the groundwork for increased regulation, the WHO FCTC, which will encourage global regulation, taken together with the possible regulation by the FDA, it seems likely that regulation of the cigarette is possible. Therefore, it is timely to canvass the optimal policies. The efforts of Philip Morris to support “tough but fair regulation” in the United States could be helpful, although it is noteworthy that Philip Morris also is seeking to “continue use of descriptors such as ‘full flavor,’ ‘light’ and ‘ultra light,’” which could undermine the potential benefits of reduced toxicants. This reinforces the importance of regulation to define reduced-risk products.

Control of carcinogens and other major toxins presents a relatively straightforward set of issues. A process of establishing the market median and setting it as the upper limit has been proposed (Gray & Boyle, 2000, 2002; Gray & Kozlowski, 2003; Gray et al., 2000). This now seems too softhearted. There can be little justification for allowing toxicant levels to be other than as low as possible. Given 2–3 years, it is likely that the tobacco industry could meet a standard upper limit, close to the current minimum, for priority substances that could include CO and several other major toxicants. It is difficult to imagine justifiable reasons for allowing unnecessarily high yields of toxicants in a consumer product. Furthermore, a regulator could be accused of negligence if higher levels were allowed. The degree of ensuing industry disruption would depend on the levels set. The outcome of levels set at, for example, 10% above the minimum yields in Table 1 would likely be a substantial shrinkage in the number of brands on the market, substantial changes in the unmanufactured tobacco market with impact on the global tobacco growing industry, and substantial change in the cigarette manufacturing industry. This level of regulation would not, however, take cigarettes off the market or deprive smokers of the choice of a desired nicotine dose. Nor would it bankrupt an industry with vast resources. In the long term, the cigarette would become simpler, as would its marketing.

The proposals described would involve both the tobacco industry and the public health community in an ongoing process of necessary collaboration, to which both are foreign. This process would have to be transparent and research based, and funded by a levy on tobacco products. It will be difficult for both sides as there is a long history of mistrust.

Regulation of nicotine would be more controversial, since agreement on the best approach is unlikely within the public health community. For this reason, the starting point would have to involve building a public health consensus, which may take some time. Nonetheless, as discussed elsewhere, without removing

nicotine or making products nonaddictive, regulation of ingredients and designs that unnecessarily increase addictiveness could be done in parallel to the present proposal to reduce toxicants (Henningfield et al., 2004).

Making these recommended changes to the product does not solve the potential problems of public perception and the potential effects that undermine cessation efforts. As long as the tobacco industry has power to advertise, these risks exist, as evidenced by claims such as “reduced carcinogens.” In countries where advertising is effectively banned (Norway, Finland, Australia, and Singapore), public health messages should prevail and can be tested. Where advertising persists (United States, Europe), regulators will need to use media access to keep the message in perspective. The difficulties of doing this should not detract from the policy proposed, but will require monitoring of public perceptions and behavior for these specific purposes. Regulation of the labeling as advocated by the WHO FCTC could also help to reduce the risk that toxin reduction would be effectively used by the tobacco industry to undermine prevention and cessation efforts. Nonetheless, it will be vital to monitor the effects to enable corrective actions to potential unintended consequences, as has been discussed elsewhere (Stratton et al., 2000).

## Conclusion

The difficulties of developing consensus around nicotine regulation are not an excuse for accepting the status quo. Control of toxicants is possible and is needed urgently. Changing the status quo to bring the tobacco industry in line with the food and pharmaceutical industries would appear to be consistent with the lessons of history. Finally, failure to embrace public health style harm reduction may leave us with a “harm reduction” regime as espoused by Philip Morris, which could ensure the status quo.

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## References

Australian Department of Health and Ageing. (2001). Australian Cigarette Emissions Data. Accessed July 1, 2004, at [http://www.health.gov.au/pubhlth/strateg/drugs/tobacco/emis\\_data.htm](http://www.health.gov.au/pubhlth/strateg/drugs/tobacco/emis_data.htm)

- Bates, C., McNeill, A., Jarvis, M., & Gray, N. (1999). The future of tobacco product regulation and labeling in Europe: Implications for the forthcoming European Union directive. *Tobacco Control, 8*, 225–235.
- Beard, M. C., Anneges, J. F., Woolner, L. B., & Kurkland, L. T. (1985). Bronchiogenic carcinoma in Olmsted County, 1935–1979. *Cancer, 55*, 2026–2030.
- Bolliger, C. T., Zellweger, J. P., Danielsson, T., van, B., X., Robidou, A., Westin, A., Perruchoud, A. P., & Sawe, U. (2000). Smoking reduction with oral nicotine inhalers: Double blind, randomized clinical trial of efficacy and safety. *British Medical Journal, 321*, 329–333.
- Connolly, G. N., Winn, D. M., Hecht, S. S., Henningfield, J. E., Walker, B., Jr., & Hoffmann, D. (1986). The reemergence of smokeless tobacco. *New England Journal of Medicine, 314*, 1020–1027.
- Cox, J. D., & Yesner, R. A. (1979). Adenocarcinoma of the lung: Recent results from the Veterans Administration Lung Group. *American Review of Respiratory Disease, 120*, 1025–1029.
- Cutler, S. J., & Young, J. L. (1975). Third National Cancer Survey: Incidence data. *Journal of the National Cancer Institute, 41*, 454.
- Devesa, S. S., Shaw, G. L., & Blot, W. J. (1991). Changing patterns of lung cancer incidence by histological type. *Cancer Epidemiology Biomarkers and Prevention, 1*, 29–34.
- Doll, R., & Hill, A. B. (1950). Smoking and carcinoma of the lung. *British Medical Journal, 2*, 739–748.
- El-Torky, M., El-Zeky, F., & Hall, J. C. (1990). Significant changes in the distribution of histologic types of lung cancer. A review of 4928 cases. *Cancer, 65*, 2361–2367.
- Fischer, S., Spiegelhalter, B., & Preussmann, R. (1990). Tobacco-specific nitrosamines in European and USA cigarettes. *Archiv Fur Geschwulstforschung, 60*, 169–177.
- Gray, N., & Boyle, P. (2000). The regulation of tobacco and tobacco smoke. *Annals of Oncology, 11*, 909–914.
- Gray, N., & Boyle, P. (2002). Regulation of cigarette emissions. *Annals of Oncology, 13*, 19–21.
- Gray, N., & Boyle, P. (2003). The future of the nicotine-addiction market. *Lancet, 362*, 845–846.
- Gray, N., & Kozlowski, L. T. (2003). More on the regulation of tobacco smoke: How we got here and where next. *Annals of Oncology, 14*, 353–357.
- Gray, N., Zaridze, D., Robertson, C., Krivosheeva, L., Sigacheva, N., & Boyle, P. (2000). Variation within global cigarette brands in tar, nicotine, and certain nitrosamines: Analytic study. *Tobacco Control, 9*, 351.
- Hammond, E. C., Garfinkel, L., Seidman, H., & Lew, E. A. (1976). “Tar” and nicotine content of cigarette smoke in relation to death rates. *Environmental Research, 12*, 263–274.
- Hecht, S. S. (1999). Tobacco smoke carcinogens and lung cancer. *Journal of the National Cancer Institute, 91*, 1194–1210.
- Henningfield, J. E., Benowitz, N. L., Connolly, G. N., Davis, R. M., Gray, N., Myers, M. L., & Zeller, M. R. (2004). Reducing tobacco addiction through tobacco product regulation. *Tobacco Control, 13*, 132–135.
- Henningfield, J. E., Benowitz, N. L., Slade, J., Houston, T. P., Davis, R. M., & Deitchman, S. D. (1998). Reducing the addictiveness of cigarettes. Council on Scientific Affairs, American Medical Association. *Tobacco Control, 7*, 281–293.
- Henningfield, J. E., & Slade, J. (1998). Tobacco-dependence medications: Public health and regulatory issues. *Food and Drug Law Journal, 53*(Suppl.), 75–114.
- Hoffmann, D., Djordjevic, M. V., & Hoffmann, I. (1997). The changing cigarette. *Preventive Medicine, 26*, 427–434.
- Hoffmann, D., & Hoffmann, I. (1997). The changing cigarette, 1950–1995. *Journal of Toxicology and Environmental Health, 50*, 307–364.
- International Agency for Research on Cancer. (1986). Evaluation of the carcinogenic risk of chemicals to humans: Tobacco smoking. Lyon, France: IARC.
- Johnson, W. W. (1988). Histologic and cytologic patterns of lung cancer in 2580 men and women over a 15-year period. *Acta Cytologica, 32*, 162–168.
- Kozlowski, L. T., O'Connor, R. J., & Sweeney, C. T. (2001). Cigarette design. *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine*. Bethesda, Maryland: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

- Peto, R. (1986). Influence of dose and duration of smoking on lung cancer rates. *IARC Scientific Publication, 12*, 23–33.
- Royal College of Physicians. (2000). *Nicotine addiction in Britain. A report of the Tobacco Advisory Group of the Royal College of Physicians*. London: Royal College of Physicians.
- Stratton, K., Shetty, P., Wallace, R., & Bondurant, S. (2001). *Clearing the smoke*. Washington, DC: Institute of Medicine.
- Tang, J. L., Morris, J. K., Wald, N. J., Hole, D., Shipley, M., & Tunstall-Pedoe, H. (1995). Mortality in relation to tar yield of cigarettes: a prospective study of four cohorts. *British Medical Journal, 311*, 1530–1533.
- Thun, M. J., & Heath, C. W. J. (1997). Changes in mortality from smoking in two American Cancer Society prospective studies since 1959. *Preventive Medicine, 26*, 422–426.
- Thun, M. J., Lally, C. A., Flannery, J. T., Calle, E. E., Flanders, W. D., & Heath, C. W. J. (1997). Cigarette smoking and changes in the histopathology of lung cancer. *Journal of the National Cancer Institute, 89*, 1580–1586.
- U.S. Department of Health and Human Services. (1981). *The health consequences of smoking: The changing cigarette. A report of the Surgeon General*. Rockville, MD: Public Health Services, Office on Smoking and Health.
- U.S. Department of Health and Human Services. (1997). *Changes in cigarette related disease risk and their implication for prevention and control*. Bethesda, MD: National Cancer Institute.
- U.S. Department of Health and Human Services. (2001). *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine*. Bethesda, MD: National Cancer Institute.
- Vincent, R. G., Pickren, J. W., Lane, W. W., Bross, I., Takita, H., Houten, L., Gutierrez, A. C., & Rzepka, T. (1977). The changing histopathology of lung cancer: a review of 1682 cases. *Cancer, 39*, 1647–1655.
- Wayne, G. F., & Connolly, G. N. (2002). How cigarette design can affect youth initiation into smoking: Camel cigarettes 1983–93. *Tobacco Control, 11*(Suppl.), I32–I39.
- Weinstein, N. D. (2001). Public understanding of risk and reasons for smoking a low-yield product. *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine* (pp.193–235). Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.
- Windsor, R., Oncken, C., Henningfield, J., Hartmann, K., & Edwards, N. (2000). Behavioral and pharmacological treatment methods for pregnant smokers: issues for clinical practice. *Journal of the American Medical Women's Association, 55*, 304–310.
- Wu, A. H., Henderson, B. E., Thomas, D. C., & Mack, T. M. (1986). Secular trends in histologic types of lung cancer. *Journal of the National Cancer Institute, 77*, 53–56.
- Wynder, E. L., & Graham, E. A. (1950). Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. *Journal of the American Medical Association, 143*, 336–338.
- Wynder, E. L., Graham, E. A., & Croninger, A. G. (1953). Experimental production of carcinoma with cigarette tar. *Cancer Research, 13*, 855–864.
- Wynder, E. L., & Muscat, J. E. (1995). The changing epidemiology of smoking and lung cancer histology. *Environmental Health Perspectives, 103*(Suppl. 8), 143–148.
- Wynder, E. L., & Stellman, S. D. (1979). Impact of long-term filter cigarette usage on lung and larynx cancer risk: a case-control study. *Journal of the National Cancer Institute, 62*, 471–477.
- Young, J. L., Percy, C. L., & Asire, A. J. (1981). *Cancer incidence and mortality in the United States, 1973–1977* (1-1081). Bethesda MD: National Cancer Institute.
- Zheng, T., Mayne, S. T., Holford, T. R., Boyle, P., Liu, W., Chen, Y., Mador, M., & Flannery, J. (1993). The time trend and age-period-cohort effects on incidence of adenocarcinoma of the stomach in Connecticut from 1955–1989. *Cancer, 72*, 330–340.