Smoking, Estrogen, and Prevention of Heart Disease in Women

Despite the remarkable decline in mortality rates from coronary heart disease (CHD) in the United States (and many other Western nations), it nevertheless remains the leading cause of death among both men and women in the United States. This need not be so. Although much remains to be learned about the causes of heart disease, application of available scientific knowledge would dramatically reduce the current high mortality rates. Risk factors for a disease often are most clearly delineated among populations with low to medium rates of occurrence; in such a situation, a modest difference in the absolute rates of disease can constitute a fairly high relative risk (or odds ratio) that is easy to discern. For heart disease, studies of young and middle-aged women are especially informative because the rates of CHD in this segment of the population are generally low.

The case-control study of CHD in young women by Beard and associates, reported in this issue of the Proceedings (pages 1471 to 1480), focused on four risk factors for heart disease: cigarette smoking, hypertension, diabetes, and lack of postmenopausal estrogens. Of great interest is the statistical analysis that provides not only the odds ratio associated with each of these factors but also an estimate of the proportion of disease potentially attributable to each factor. It is important to realize that these proportions need not total 100%. Because CHD is multifactorial, interventions at several points are possible, whereas the potential reduction in the rate of disease is calculated for each intervention alone. Thus, according to the data of Beard and colleagues, elimination of smoking in this population might reduce CHD by as much as 64%, elimination of hypertension as a risk factor would reduce CHD by 45%, and use of estrogen replacement in all eligible women could reduce the rate of CHD by 45%.

Because cigarette smoking is associated with such a pronounced elevated risk of CHD and because the prevalence of this practice remains high, cigarette smoking must be regarded as the leading avoidable cause of heart disease. In the population of young women in Rochester, Minnesota, Beard and co-workers found that cigarette smokers had about 5 times the risk of definite CHD in comparison with those who had never smoked. This substantial increase in risk is consistent with other data from women of comparable age. For example, in the Nurses Health Study cohort of more than 120,000 US female nurses, current smokers had approximately a twofold to threefold increase in risk of nonfatal myocardial infarction and CHD-related death. A pronounced dose effect was apparent in that study, with relative risks of 4.2 for smokers of 15 to 24 cigarettes per day and 10.8 for women who smoked 45 or more cigarettes per day. Even women smoking as few as one to four cigarettes per day experienced a statistically significant doubling in risk. In that study, half the cases of CHD were attributable to smoking. Beard and associates were unable to assess the effects of cessation of smoking, but other investigators have demonstrated that the bulk of the excess risk disappears after a year or two.

The finding of an excess risk of heart disease associated with smoking is not new, but the magnitude of the effect is still not widely appreciated either among health-care professionals or by the general public. Beard and colleagues, and other investigators as well, have convincingly demonstrated that elimination of smoking can reduce the rate of major heart disease by half or more in young and middle-aged women. This point merits continued emphasis for physicians and other health-care professionals for several reasons. Unlike treatment for other risk factors,
cessation of smoking is essentially without risk (the minor weight gain that often accompanies cessation constitutes a negligible increase in risk) and reduces the risk of a host of adverse effects. Cessation of smoking is free, or at least relatively inexpensive, and, once accomplished, requires no ongoing attention, in contrast to long-term, perhaps lifelong, treatment of hypertension or dyslipidemias.

Cigarette smoking does not receive the degree of attention corresponding to its importance as a coronary risk factor. In part, this quietude exists because it is no longer considered newsworthy. Some of the silence, however, must be attributed to the influence of the tobacco industry. In a careful analysis, Warner showed that discussions of the health consequences of smoking were muted in the print media because tobacco advertising is such an important source of revenue. In contrast, the smoking-cessation “industry” is small and stands to gain much less than the large pharmaceutical companies in promoting treatments for other coronary risk factors. For these reasons, a considerable burden falls to the health-care provider to promote cessation of smoking.

Although almost everyone knows that smoking is harmful, patients are often unable to put into perspective the various and widely publicized health risks of all sorts. Silence from the physician about the adverse effects of smoking may well be interpreted by the patient as a tacit statement that it is not actually so detrimental. Because cigarette smoking is an addiction, quitting can be difficult, and physicians may often despair that their exhortations have no effect other than to arouse resentment. Although it is true that only a small fraction of patients advised to quit will do so forthwith, it is also well established that advice from a physician or other health-care provider does have an important effect in the long term. Patients with an illness may be particularly receptive to such advice. Nor should the physician despair that many quitters resume smoking after a short period of abstinence. In many cases, cigarette smokers will quit permanently after another try or two at cessation. Quitting smoking, like many other activities, benefits from practice. The decline in the prevalence of smoking in the past few years is gratifying; physicians must continue to be at the forefront in encouraging this reduction, both in public forums and through individual patient contact.

Simple admonition is important but not sufficient. Health-care providers must be prepared to supply information on techniques for quitting smoking to those who are ready to consider them. The Office on Smoking and Health, part of the United States Public Health Service, is a valuable resource for this information; their address is Public Information Branch, Room 1-18 Park Building, 5600 Fishers Lane, Rockville, MD 20857 (telephone number 301-443-1690). Another valuable resource is the National Heart, Lung, and Blood Institute Education Programs Information Center, at 4733 Bethesda Avenue, Suite 530, Bethesda, MD 20814 (telephone number 301-951-3260). That office will send to physicians free copies of a useful booklet entitled “Clinical Opportunities for Smoking Intervention: A Guide for the Busy Physician.” In addition, the general public can call a toll-free number at the National Cancer Institute for tips on cessation of smoking and for information on a variety of smoking-cessation programs in their local area: 1-800-422-6237.

Women have unique incentives to stop smoking. Young women should be reminded of the dangers to the fetus; even if a pregnancy is not planned for the immediate future, it would be wise to quit smoking well in advance of a pregnancy because the longer one smokes, the more difficult it becomes to quit. In addition, women who smoke have an earlier menopause. The effect is dose related; heavy smokers go through menopause about 2 years earlier than nonsmokers. Although this effect of smoking may not in itself be an inducement to quit, if viewed as demonstrating the damage of smoking to the ovary, it may provide additional cause for concern among female smokers. The menopause-promoting effect of smoking may also be linked to the decreased fertility among women who smoke.

Smoking prevalence among women is higher now than it was several decades ago, and women
are beginning to smoke cigarettes at younger ages. Nonetheless, some trends are encouraging. Younger cohorts of women are quitting smoking at faster rates than earlier birth cohorts of the same age. Moreover, the overall rates of cessation of smoking have been increasing in recent years.

Consistent with a large and growing body of literature, Beard and co-workers observed a 45% decreased risk of CHD among women who had ever used estrogens. Although the benefit did not reach statistical significance, this result is most likely attributable to the small size of the study and to the relatively infrequent use of estrogens. The relative risk of CHD for women who had ever used estrogens was 0.55 (95% confidence interval, 0.24 to 1.30). In this population, Beard and associates estimate that approximately 14% of myocardial infarctions were prevented by use of estrogen (if a causal relationship is assumed to be present) and that 45% of cases might be avoided if estrogen replacement was used in all eligible women.

The epidemiologic data on postmenopausal estrogens and CHD have been controversial, but the inconsistencies in the findings have been more apparent than real. Besides the study by Beard and colleagues, more than 20 published epidemiologic studies have addressed this issue. In most of these investigations, estrogen use was found to be associated with a reduction in the rate of CHD of 40% or more. Only two studies yielded essentially null results, and in two additional studies, an elevated risk was observed.

The two studies with null findings were hospital-based case-control studies conducted by Rosenberg and co-workers. In the first study, the investigators initially observed a relative risk of 0.5, but after adjusting for an array of factors including hospital site and religion, the relative risk was changed to 1.0. Only 8 of the 336 cases were current users of estrogens. Results from hospital-based case-control studies can be difficult to interpret because of the problems of selecting control subjects from among patients with illnesses supposedly unrelated to estrogen use. For example, in the second study by Rosenberg and associates, women with fractures were used as control subjects; we now know that this study design was inappropriate because estrogens reduce the risk of fracture. Even illnesses with no biologic relationship to estrogens may be inappropriate for use as controls in instances in which physicians might be reluctant to add yet another medication.

The hospital-based case-control study with an increased risk for myocardial infarction was conducted by Jick and colleagues, who observed a relative risk of 4.2 (95% confidence interval, 1.0 to 18.8) among postmenopausal women. There were only 14 cases among postmenopausal women—too few to draw firm conclusions. Moreover, of the 17 cases that entered the analysis, 16 were cigarette smokers.

In the Framingham study, Wilson and co-workers also reported an increase in risk of cardiovascular disease associated with use of estrogens. Of 11 prospective cohort studies, this is the only one that did not report a decreased risk among estrogen users. They found a statistically significant relative risk of 1.76 for all cardiovascular outcomes, including angina, intermittent claudication, and transient cerebral ischemia. Despite this apparently increased risk, total mortality was unaffected (relative risk of 0.97). The apparent increase in risk was not statistically significant when only myocardial infarction was considered. Also, the statistical adjustment for total and high-density lipoprotein cholesterol was inappropriate because alteration of these variables is the most plausible mechanism of action for estrogen. Only 302 women had ever used estrogens in that study population. A reanalysis of the Framingham data with use of more specific endpoints (myocardial infarction, coronary insufficiency, and coronary-related death) showed a protective effect among women 50 to 59 years of age, with a relative risk of 0.4, and no effect among older women (relative risk of 1.1).

Apart from the aforementioned four studies, all other epidemiologic investigations have found a decreased risk of CHD among estrogen users. In particular, all the population-based case-control studies had relative risks that
ranged from 0.3 to 0.7. In some of those studies, particularly the smaller ones such as that by Beard and associates, the apparent benefit did not attain statistical significance. Nonetheless, the trend toward protection is clear.

If one considers the reanalysis of the Framingham data, then all the prospective studies are consistent in observing an apparent protective effect from use of estrogens. For example, in the Nurses Health Study, 32,317 postmenopausal women, who were 55 years of age or younger at baseline, were followed for 2 to 4 years for the occurrence of nonfatal myocardial infarction or death due to coronary disease. Approximately half had used hormones at some point; in these women, a relative risk of 0.5 was observed in comparison with women who had never used hormones.

The benefits are not limited to younger postmenopausal women. In their landmark study of residents of the Leisure World retirement community in California, Henderson and colleagues found that all-cause mortality was significantly reduced by 20% (relative risk of 0.80; 95% confidence interval, 0.70 to 0.91) among women who had used estrogen replacement therapy. Much of the reduction was due to a lower rate of fatal myocardial infarctions; the relative risk for those who had ever used estrogen was 0.59 (95% confidence interval, 0.42 to 0.82). This study is notable for the large number of endpoints, 1,019 total deaths and 149 fatal infarctions, leading to substantial statistical power and precise estimates of effect. The median age of the subjects in this study was more than 75 years.

Evidence in support of a protective effect of estrogens for CHD also is derived from investigations that have used other study designs. Only one randomized trial has been reported; a relative risk of 0.3 was observed for myocardial infarction, but the study was small (only 84 study subjects) and the finding was not statistically significant. In two large cross-sectional studies of women who underwent coronary angiography, the degree of atherosclerosis was substantially and significantly reduced in women taking estrogens.

In the Nurses Health Study, the Leisure World study, and several others, the benefit from estrogens was more pronounced among current users. In the Nurses Health Study, among current users of estrogen the relative risk was 0.3 (95% confidence interval, 0.2 to 0.6), whereas for past users it was 0.7 (95% confidence interval, 0.4 to 1.2). In the Leisure World study, the relative risk for fatal myocardial infarction was 0.47 among current users and 0.62 for past users of estrogen. In addition, neither study observed an increasing degree of protection with increasing duration of use. Collectively, these findings suggest that protection may begin soon after the initiation of estrogen therapy and declines soon after cessation. Further work is needed to define the time frame over which estrogens may be effective for prevention of coronary disease.

The most plausible and best supported mechanism of action for this benefit is the effect of estrogens on the lipid profile. Estrogens decrease low-density lipoprotein cholesterol and raise high-density lipoprotein cholesterol substantially. This effect has been demonstrated repeatedly in cross-sectional studies and clinical trials. One cannot rule out other possible mechanisms, particularly because estrogen receptors are present in the circulatory system.

One major current issue is the effect of added progestins on risk of CHD. In women with intact uteri, the addition of a progestin to the estrogen regimen is often recommended to reduce or eliminate the excess risk of uterine cancer due to taking unopposed estrogen. Clinical investigations, however, have consistently shown that the benefits of estrogen on the lipid profile are attenuated with the addition of progestins. Differences in the degree of this attenuation have been observed between various progestin formulations and dosage regimens, and a remaining challenge is to provide protection from uterine cancer without undermining the benefits of estrogen for heart disease.

Beard and associates have demonstrated that a substantial proportion of heart disease in women is attributable to several risk factors: hypertension, diabetes, cigarette smoking, and, in postmenopausal women, lack of estrogen.
These investigators were unable to assess the influence of other important modifiable risk factors such as diet, blood lipids, and physical inactivity. Clearly, we must continue our efforts to learn more about the causes of heart disease, but by fully applying currently available knowledge, we already have the capability to reduce substantially the mortality rate from CHD.

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REFERENCES