Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk

April 2009

Executive Summary

A significant gap exists in the integration of our knowledge on tobacco smoke and breast cancer. Three authoritative reviews of active smoking and breast cancer have been published since the year 2000, but they considered only data published up until 2002. Since 2002, at least 40 more epidemiologic studies have been published on various aspects of smoking and breast cancer, including two major reports on secondhand smoke (SHS) and breast cancer and at least 6 meta-analyses. Unfortunately, the conclusions from the reviews have not been consistent, and some did not seem compatible with recently published evidence.

In light of the controversy, an Expert Panel was convened with the mandate to comprehensively examine the evidence regarding the possible relationship between tobacco smoke and breast cancer and answer the following questions:

- What can be concluded from current knowledge about the nature of the relationship between tobacco smoke (both SHS and active exposure) and pre- and postmenopausal breast cancer?
- Can the amount of breast cancer incidence and mortality attributable to active and SHS be estimated?
- What further research is needed to better understand the relationship between tobacco smoke and breast cancer?
- Does the Expert Panel wish to make any other comments in the light of the conclusions they have reached about the nature of the relationship between tobacco smoke and breast cancer?

Toxicology and Biological Mechanisms

According to the International Agency for Research on Cancer (IARC), there are 20 known or suspected mammary carcinogens in tobacco smoke. The Panel concurred with earlier assessments that there were biological mechanisms that explain how exposure to the carcinogens in tobacco smoke could lead to breast cancer.

Active Smoking and Breast Cancer

Historically, the epidemiological evidence concerning breast cancer and smoking was conflicting, with some studies showing increase in risk and others not. Recent studies, particularly a number of cohort studies, have added to the weight of evidence suggesting that early age of smoking commencement is associated with an increase in breast cancer risk of 20%. These cohort studies in particular have also added to the evidence suggesting that higher pack-years of smoking and longer duration of smoking may increase risk 10 to 30%.

However, the strongest evidence for an active smoking risk resulted from studies examining smoking and genetics. Three recent meta-analyses and a pooled analysis have found 35% to 50% increases in breast cancer risk for long-term smokers with one of several *N-acetyltransferase 2* (*NAT2*) slow acetylation genotypes. NAT2 is an enzyme which functions to both activate and deactivate carcinogens in the body. About half of North American women have a *NAT2* slow acetylation genotype, depending on ethnicity.

The most recent and extensive of the three meta-analyses (published in 2008) synthesized 13 studies and was particularly persuasive: among women with a *NAT2* slow acetylator genotype, those who had smoked had an estimated 27% increase in risk of breast cancer compared to women who had never smoked (RR 1.27; 95% CI 1.16-1.39), whereas women with a *NAT2* fast acetylation genotype had no increase in risk. Furthermore, among women with a *NAT2* slow acetylator genotype, the pooled analysis and meta-analysis produced estimates of 44% and 49% increases in breast cancer risk for women who reported 20 or more pack-years of smoking compared to never active-smokers
(RR of 1.44 (95% CI 1.23-1.68) and 1.49 (95% CI 1.08-2.04), respectively). Results were consistent for both pre- and postmenopausal breast cancer; dose-response relationships were observed with pack-years and smoking duration; recall bias was judged unlikely; the authors did not observe apparent publication bias; and there are biological mechanisms that support the observed risk pattern.

Further, a recent report on a collaborative case–control study of women under age 50 who were carriers of mutations in *BRCA1* and *BRCA2* among breast cancer registries in the United States, Australasia, and the Ontario Cancer Genetics Network, found a doubling of risk of breast cancer associated with five or more pack-years of smoking. Although a single study, it was of better design than several similar earlier studies that did not observe increased risk and provides further support for the conclusion that there are subgroups of women who are more sensitive to tobacco smoke than other women.

Secondhand Smoke and Breast Cancer Risk

Both the California Environmental Protection Agency (CalEPA) (in 2005) and the U.S. Surgeon General (in 2006) published meta-analyses that suggested a 60-70% increase in breast cancer risk

among younger/primarily premenopausal women who had never smoked, associated with regular long-term exposure to SHS. Based on their assessment of the toxicologic and the epidemiologic weight of evidence for both SHS and active smoking as well as their understanding of biologic mechanisms, the CalEPA concluded that the relationship between SHS and breast cancer among younger, primarily premenopausal women was consistent with causality. The Surgeon General concluded that the evidence was suggestive, but not sufficient to conclude there was a causal relationship, based in particular on the lack of an established causal relationship between active smoking and breast cancer.

A meta-analysis of five studies with good measurement of lifetime exposure to active and SHS found that each about doubled the risk of premenopausal breast cancer. Most other studies, obtaining only a partial assessment of lifetime SHS exposure or not collecting it at all (comparing smokers to nonsmokers without taking account of SHS exposure) likely underestimate the true risk of both active and SHS for breast cancer.

Conclusions

Causality

Active Smoking
Based on the weight of evidence from epidemiologic and toxicological studies and understanding of biological mechanisms, the associations between active smoking and both pre- and postmenopausal breast cancer are consistent with causality.

Secondhand Smoke
The association between SHS and breast cancer in younger, primarily premenopausal women who have never smoked is consistent with causality. The evidence is considered insufficient to pass judgement on SHS and postmenopausal breast cancer.

Attributable Risk

It would be premature at this time to estimate the magnitude of breast cancer incidence and mortality attributable to active and SHS; this could be a topic for further research.

Research Recommendations

Further research would help to better understand and quantify the tobacco-breast cancer risks, such as: carefully designed case-control and cohort studies with comprehensive measures of lifetime exposure to tobacco smoke, as well as measures of exposure at targeted periods of suspected increased susceptibility, e.g., puberty until giving birth for the first time; quantitative meta-analyses focusing on risk related to age at smoking initiation, smoking before pregnancy, and high duration/ high pack-years smoking; further research to better understand the dynamics

between active and passive risk, and further study of tobacco risk related to targeted genotypes, particularly *NAT2* and to the *BRCA1* and *BRCA2* mutation.

Other Considerations

Tobacco smoke is one of the few modifiable risks for breast cancer and it impacts many women. Young women in particular, should understand that available evidence suggests that the relationship between breast cancer and both active smoking and SHS is consistent with causality. Many young women are exposed to SHS, many continue to take up smoking at a young age, and the average age of first childbirth is older than in the past, which may extend the period of enhanced vulnerability. The public health implications of these findings highlight the need for effective messaging.