

UC San Francisco

Reports on Industry Activity from Outside UCSF

Title

Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk

Permalink

<https://escholarship.org/uc/item/5x79f22t>

Publication Date

2009-04-01

Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk

Neil E. Collishaw (Chair)

Norman F. Boyd

Kenneth P. Cantor

S. Katharine Hammond

Kenneth C. Johnson

John Millar

Anthony B. Miller

Mark Miller

Julie R. Palmer

Andrew G. Salmon

Fernand Turcotte

April 2009

Collishaw NE (Chair), Boyd NF, Cantor KP, Hammond SK, Johnson KC, Millar J, Miller AB, Miller M, Palmer JR, Salmon AG, Turcotte F. *Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk*. Toronto, Canada: Ontario Tobacco Research Unit, OTRU Special Report Series, April 2009.

Expert Panel Members

Norman F. Boyd, D.Sc., M.D., F.R.C.P (C)
University of Toronto
The Campbell Family Institute for Breast Cancer Research
Ontario Cancer Institute

Kenneth P. Cantor, Ph.D., M.P.H.
Senior Investigator
Division of Cancer Epidemiology and Genetics
United States National Cancer Institutes

Neil E. Collishaw, M.A. – Chair
Research Director
Physicians for a Smoke-Free Canada

S. Katharine Hammond, Ph.D.
Professor of Environmental Health Sciences
School of Public Health, University of California, Berkeley

Kenneth C. Johnson, Ph.D.
Research Scientist
Evidence and Risk Assessment Division
Centre for Chronic Disease Prevention and Control
Public Health Agency of Canada

John Millar, B.Sc., M.HSc., M.D., F.R.C.P (C)
Executive Director, Population Health
Provincial Health Services Authority
Vancouver, British Columbia

Anthony B. Miller, M.D., F.R.C.P (C), F.R.C.P.
Associate Director, Research
Dalla Lana School of Public Health
University of Toronto

Mark Miller, M.D., M.P.H.
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Oakland, California, and
Director, Paediatric Environmental Health Specialty Unit
University of California, San Francisco

Julie R. Palmer, Sc.D., M.P.H.
Professor of Epidemiology
Boston University School of Public Health
Slone Epidemiology Center at Boston University

Andrew G. Salmon, M.A., D.Phil
Chief, Air Toxicology and Risk Assessment Division
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Oakland, California

Fernand Turcotte, M.D., M.P.H., F.R.C.P (C)
Professor Emeritus, Public Health in the Department of
Social and Preventive Medicine in the Faculty of Medicine
at Laval University in Quebec

Disclaimer: Views expressed in this report represent those of the Panel members and do not necessarily represent the views of the respective institutions for whom they work.

Acknowledgements

The Panel would like to thank the Public Health Agency of Canada, and the Ontario Tobacco Research Unit for financial support. The Panel is especially grateful to the Ontario Tobacco Research Unit for including the Expert Panel's November 10-11, 2008 meeting as part of the larger conference, *Tobacco Control for the 21st Century: Challenges in Research and Evaluation*. The Panel is also grateful to Physicians for a Smoke-Free Canada and the Canadian Partnership Against Cancer for their contributions of staff time and support of the project. We would also like to acknowledge Jodi Wilson for extensive background research and technical support, Meagan Loftin, Robert Burton and Howard Morrison for editorial input and Marilyn Pope and Sonja Johnston for final formatting.

Table of Contents

Expert Panel Members.....	iii
Acknowledgements.....	iv
Table of Figures.....	vi
Table of Tables.....	vii
General Abbreviations Used in This Report.....	viii
Genetic Abbreviations Used in This Report.....	viii
Executive Summary.....	1
1. Introduction.....	5
2. Evidence Evaluation.....	7
3. Background – Other Risk Factors for Breast Cancer.....	8
4. Active Smoking and Secondhand Smoke Exposure Epidemic in North America in the 20th Century.....	9
5. Differing Toxicities of Mainstream Smoke, Sidestream Smoke and Secondhand Smoke.....	11
6. Active Smoking and Secondhand Smoke Cause Other Cancers and Chronic Diseases.....	12
7. Toxicology and Breast Cancer.....	12
8. Biological Mechanisms.....	14
9. Epidemiological Studies of Active Smoking and Breast Cancer.....	16
9.1 Collaborative Group on Hormonal Factors in Breast Cancer - Meta-analysis of Smoking, Alcohol and Breast Cancer, 2002.....	16
9.2 Active Smoking Duration and Pack-Years.....	20
9.3 Cigarette Smoking Before a First Full-term Pregnancy.....	36
9.4 Age at Initiation of Smoking.....	39
10. Epidemiologic Studies of Active Smoking and Genetics.....	40
10.1 Smoking and BRCA1 and BRCA2.....	40
10.2 Smoking, Familial History of Breast Cancer and Breast Cancer Risk.....	42
10.3 Smoking, Genotypes and Breast Cancer Meta-analyses.....	43
10.4 NAT2 Slow Acetylator Genotype and Active Smoking: Application of Causality Criteria... ..	47
10.5 Panel’s Judgement on Active Smoking and Breast Cancer Risk.....	49
11. Secondhand Smoke.....	49
11.1 Secondhand Smoke and Breast Cancer Literature.....	50
11.2 More Recent Studies of SHS and Premenopausal Breast Cancer.....	52
11.3 Causal or Suggestive? The Debate Over the Evidence.....	54
11.4 Panel’s Judgement on Secondhand Smoke Exposure and Breast Cancer Risk.....	57
12. Other Considerations.....	57
13. Conclusions.....	57
14. References.....	59
Appendix 1: Summary of Epidemiological Reviews and Meta-Analyses Assessing the Association between Breast Cancer and Tobacco Smoke, 1993-2008.....	67

Table of Figures

Figure 1: Smoking in Canada, 1965-2007	10
Figure 2: Percentage of Adults Age ≥ 18 Years Who Are Current Cigarette Smokers, by Sex – United States, 1955-1993	10
Figure 3: Breast Cancer Risk for Ever vs Never Smokers Among Women Who Reported Drinking No Alcohol.....	17
Figure 4: Meta-analysis of Studies Assessing the Effect of Smoking Before/During First Pregnancy with Breast Cancer Risk.....	36
Figure 5: Estimated Cumulative Risk of Breast Cancer for BRCA1 and BRCA2 Mutation Carriers to Age 50	41
Figure 6: Meta-Analysis of Slow NAT2 Acetylators, Smoking and Breast Cancer Risk for Higher Person-years of Smoking.....	45
Figure 7: Meta-analysis of Secondhand Smoke and Breast Cancer Risk in Younger, Primarily Premenopausal Women Who Never Smoked	51

Table of Tables

Table 1: Ratios of Some Toxic Chemicals and Carcinogens in Undiluted Sidestream Smoke vs Mainstream Smoke.....	11
Table 2: Mammary Carcinogens Present in Environmental Tobacco Smoke	13
Table 3: Comparison of Breast Cancer Risks: Oxford 2002 Ever vs Never (Active) Smoker Risk vs Longest Duration Risk Where Alcohol Was Controlled	19
Table 4: Population-based Case-control Studies of Cigarette Smoking and Breast Cancer Risk.....	21
Table 5: Prospective Cohort Studies of Cigarette Smoking and Breast Cancer Risk	22
Table 6: Cohort Studies of Active Smoking and Breast Cancer, Risk by Smoking Duration	26
Table 7: Case-Control Studies of Active Smoking and Breast Cancer - Smoking Duration.....	28
Table 8: Cohort Studies of Active Smoking and Breast Cancer, Risk by Pack-Years	31
Table 9: Case-Control Studies of Active Smoking and Breast Cancer -Smoking Pack-years.....	33
Table 10: Case-control Studies Reporting Results on Age at Initiation of Cigarette Smoking in Relation to Breast Cancer Risk.....	38
Table 11: Cohort Studies Reporting Results for Cigarette Smoking Before First Full-term Pregnancy in Relation to Breast Cancer Risk by Year.....	38
Table 12: Case-control Studies Reporting Results on Age at Initiation of Cigarette Smoking in Relation to Breast Cancer Risk.....	39
Table 13: Cohort Studies Reporting Results on Age at Initiation of Cigarette Smoking in Relation to Breast Cancer Risk.....	40
Table 14: Association Between Smoking History and Risk of Breast Cancer by Family History of Breast Cancer in First Degree Relatives (Sisters or Mother).....	42
Table 15: Summary of Meta-Analyses by Terry and Goodman (2006) of Breast Cancer Smoking and Genotype	44
Table 16: Summary of Meta-Analysis and Pooled Analysis of Smoking Pack-years, NAT2 Acetylators Status, Menopausal Status and Breast Cancer Risk	46
Table 17: Summary Risk Estimates for Breast Cancer Risk Associated with Ever Regular Secondhand Smoke Exposure in the California EPA and U.S. Surgeon General's Reports	52

General Abbreviations Used in This Report

BMI	body mass index
CalEPA	California Environmental Protection Agency
CI	confidence interval
CTUMS	Canadian Tobacco Use Monitoring Survey
EPA	Environmental Protection Agency
ETS	environmental tobacco smoke
IARC	International Agency for Research on Cancer
OC	oral contraceptive
OR	odds ratio
RR	relative risk
SHS	secondhand smoke (also known as environmental tobacco smoke (ETS), involuntary smoking, passive smoking)

Genetic Abbreviations Used in This Report

BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CYP1A1	Cytochrome P450, family 1, subfamily A, polypeptide 1 protein
CYP1A2	Cytochrome P450, family 1, subfamily A, polypeptide 2 protein
CYP1B1	Cytochrome P450, family 1, subfamily B, polypeptide 1 protein
DNA	Deoxyribonucleic acid
GSTM1	Glutathione S-transferase Mu 1 gene
GSTT1	Glutathione S-transferase theta 1 gene
HBEC	Human-based evolutionary computation
NAT1	N-acetyltransferase 1
NAT2	N-acetyltransferase 2
NNK	4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanone
NOS3	Nitric oxide synthase 3
PAH	Polycyclic aromatic hydrocarbon
P53	tumor protein 53, tumor suppressor gene
SOD2	Superoxide dismutase 2, mitochondrial gene
SULT1A1	Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1 gene
SULT1A2	Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2 gene
SULT1B1	Sulfotransferase family, cytosolic, 1B, member 1 gene
XRCC1	X-ray repair complementing defective repair protein
XPD	xeroderma pigmentosum D protein

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.

1. Introduction

The Need for an Expert Panel on Breast Cancer and Tobacco Smoke

The gap that exists in the integration of our knowledge on tobacco smoke and breast cancer is substantial. Before 1993 more than 50 epidemiological studies had examined the relationship between tobacco smoke and breast cancer, although the quality of the studies varied greatly. The results of the better-quality studies were equivocal and the general conclusion was that no causal relationship could be established between exposure to tobacco smoke and breast cancer (Palmer, 1993). Of the three reviews of active smoking and breast cancer that have been published since the year 2000, none considered data published after 2002 (Terry and Rohan, 2002; International Agency for Research on Cancer, 2004; U.S. Department of Health and Human Services, 2004). Since 2002, at least 40 more original epidemiologic studies, including 6 meta-analyses and 2 major reports have been published on various aspects of smoking and breast cancer, helping to clarify the relationships identified in one of the 2002 reviews (Terry and Rohan, 2002).

Recently, both the California Air Resources Board and the United States Surgeon General have reported on the relationship between breast cancer and SHS (California Environmental Protection Agency, 2005; U.S. Department of Health and Human Services, 2006). The Surgeon General's Report paid less attention to the relationship between breast cancer and active smoking because this was not part of its mandate, however, the CalEPA did include an appendix on active smoking in their 2005 report.

To address this growing body of literature, during 2008 four Canadian agencies, the Ontario Tobacco Research Unit, the Public Health Agency of Canada, Physicians for a Smoke-Free Canada and the Canadian Partnership Against Cancer pooled their efforts to organize an Expert Panel. Six Canadian and five American experts were invited and agreed to participate as members of the Expert Panel. All eleven are joint authors of this report. Their names and affiliations are shown on page iii.

The purpose of this report of the Expert Panel is to provide an up-to-date synthesis of current knowledge of breast cancer and exposure to tobacco smoke, focusing on the extensive new research in the area and examining active smoking and exposure to secondhand smoke (SHS) and their association with both premenopausal and postmenopausal breast cancer.

The Work of the Expert Panel

Prior to the deliberations of the Panel, the secretariat assembled the existing literature and prepared a 60-page background document that summarized the breast cancer and tobacco literature and highlighted key original research, meta-analyses and reviews since the year 2000. That document and key papers were circulated to Panel members for review in advance of the formal Panel meeting. The Panel met for two days on November 10th and 11th, 2008 in Toronto. One member was unable to attend but contributed to all other Panel activities (S.K. Hammond). This meeting took place in the

larger context of the Conference, *Tobacco Control for the 21st Century: Challenges in Research and Evaluation*, a research conference organized and sponsored by the Ontario Tobacco Research Unit. On November 10th, 2008, presentations, discussion and debate predominated. On November 11th, 2008, the background document and related materials were examined and the Panel reached consensus on answers to the questions that had been posed to it. Observers were permitted to attend the Panel's deliberations.

Over the following months, the Panel's report was drafted by the secretariat and redrafted by Panel members, with the final version completed in April, 2009.

The organizers asked the Expert Panel to provide answers to the following questions:

1. What can be concluded from current knowledge about the nature of the relationship between tobacco smoke and breast cancer in each of the following categories?
 - a. Active smoking
 - i. Premenopausal breast cancer
 - ii. Postmenopausal breast cancer
 - b. Passive smoking
 - i. Premenopausal breast cancer
 - ii. Postmenopausal breast cancer
2. Can breast cancer incidence and mortality attributable to active smoking and SHS exposure be estimated? If so, what are those estimates?
3. What further research is needed to better understand the relationship between tobacco smoke and breast cancer?
4. 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?

Guide to This Report

We begin with short sections on evidence evaluation, breast cancer risk factors, the prevalence of smoking in the 20th century in North America, the relative toxicity of active and secondhand smoke (SHS), and the impacts of active smoking and SHS on other cancers and chronic diseases (Sections 2 to 6). Sections 7 and 8 summarize the toxicological evidence and biological mechanisms supporting a tobacco smoke-breast cancer risk. Section 9 details the epidemiologic evidence on active smoking and breast cancer. We summarize the evidence related to: long duration of smoking, pack-years of smoking, smoking before first full-term pregnancy and age at smoking initiation. Section 10 examines genetics, smoking and breast cancer. We first briefly highlight provocative research on smoking and *BRCA1* and *BRCA2* and then summarize three meta-analyses of smoking, genotype and breast cancer, with a particular focus on the 2008 meta-analysis of the *NAT2* polymorphism. Section 11 examines SHS and breast cancer risk among never smokers. We highlight recent meta-analyses from the CalEPA and the U.S. Surgeon General, and discuss the scientific debate over the strength of that evidence. Section 12 briefly addresses other considerations and Section 13 summarizes the Panel's conclusions.

2. Evidence Evaluation

The Expert Panel assessed breast cancer risk related to tobacco smoke exposure based on the weight of evidence from epidemiologic studies, toxicological studies and current understanding of biologic mechanisms. We made use of standard criteria for judging the strength of the evidence as described by the U.S. Surgeon General (2004), the International Agency for Research on Cancer (IARC) (2004) and the California Environmental Protection Agency (CalEPA, 2005). The criteria from these three sources are similar adaptations of the criteria used in the Surgeon General's original 1964 report on smoking which were an adaptation of the criteria developed by Sir Austin Bradford Hill. Five of the nine criteria Hill listed were used in the 1964 Surgeon General's Report for establishing causation: strength, consistency, specificity, temporality and coherence of an observed association. Hill also listed dose-response, plausibility, experiment and analogy. These criteria were used "to integrate multiple lines of evidence, coming from chemical and toxicologic characterizations of tobacco smoke and its components, epidemiologic approaches, and clinical investigations" (U.S. Department of Health and Human Services, 2004). The CalEPA (2005) provides a detailed review of each of these criteria and their application to risk associated with secondhand tobacco smoke.

The Expert Panel applied this weight-of-evidence approach to determine whether there was sufficient evidence for a causal association between active smoking or SHS exposure and breast cancer. We summarized the literature up to November 2008, obtaining copies and extracting risk estimates for all published studies on breast cancer and tobacco smoke that we could locate. To identify studies we made use of reviews of tobacco smoke and breast cancer by Terry and Rohan (2002), IARC (2004), the Surgeon General (2004) and the CalEPA (2005) for active smoking and the CalEPA (2005) and the Surgeon General (2006) for SHS. We used PubMed to carry out electronic searches of the literature primarily to locate studies published since these reports.

In making its scientific judgment, the Panel applied these causal criteria and considered the weight-of-evidence, which integrated the results of epidemiological studies, toxicology studies, gene-environment interactions, biomarker studies, and an understanding of biological mechanisms. Methodological issues considered in the critical review of epidemiologic literature included the number and quality of individual studies, the extent to which the analysis or design took into account potential confounders, selection bias, the potential for exposure misclassification, prospective or retrospective assessment of exposure, and study power. When studies were of otherwise similar quality, cohort studies were given more weight than case-control studies because the cohort design has the advantage of avoiding the possibilities of selection bias or recall bias.

Accurate ascertainment of tobacco smoke exposure was considered fundamental to the quality of both case control and cohort studies. Reflecting the state of epidemiology at the time, the Bradford-Hill criteria omitted consideration of the quality of exposure assessment, a critical factor which has become increasingly important in recent years in studies of environmental and occupational exposures. The studies deemed of highest quality with respect to exposure were those with "lifetime exposure ascertainment" for SHS exposure among never smokers and duration and intensity of

smoking for active smokers. For active smoking, studies that closely assessed risk related to age at smoking initiation, smoking before first pregnancy, years of smoking duration and intensity of smoking (often combined as pack-years) were deemed to have enhanced study quality.

For SHS exposure assessment, studies that collected a quantified lifetime assessment of SHS exposure, including childhood, adult residential and adult occupational histories of SHS exposure were considered to have enhanced quality. Studies utilizing quantified metrics of SHS exposure such as smoker-years of exposure were deemed to enhance study quality. For analysis of SHS risk among never smokers, studies that consistently used women without regular SHS exposure as a child or as an adult either residentially or occupationally as the referent unexposed group, were considered of better quality than studies that did not. (For example, some studies ignored occupational SHS exposure when analyzing residential SHS exposure, and vice-versa, thus contaminating the “unexposed” referent group.) Studies that reported results stratified by menopausal status at the time of diagnosis (and which had adequate sample size) were preferred.

We focused on both individual study results as well as evidence and assessments from published meta-analyses and pooled studies when available. For SHS, we carefully reviewed the evidence presented by the CalEPA (2005) and the Surgeon General (2006) on breast cancer and SHS, as well as examining literature on the subject published since those reports. Where meta-analyses or pooled studies were available, additional evidence from individual studies published since meta-analyses was also examined. Published meta-analyses and pooled studies were used as the primary tool for summarization and assessment of smoking and genetic studies. Individual studies of genotype and tobacco smoke often have small numbers of subjects in individual subgroups of exposure and genotype, there are often several genotypes studied, and there were limits on the time and resources available to the Expert Panel and the scope of mandate.

To keep the report succinct and avoid a large amount of duplication, we refer the reader to the IARC report (2004), the two Surgeon General reports (2004; 2006), the CalEPA report (2005) and the review by Terry and Rohan (2002) for short review, commentary and evaluation of many of the individual studies that contribute to various assessments. In this document we provide individual assessment of specific studies where the Panel felt the findings were particularly relevant, and for some key studies published since the earlier reviews. This report integrates these previous reports with a careful evaluation of the scientific evidence from multiple disciplines.

3. Background – Other Risk Factors for Breast Cancer

Breast cancer is the most commonly diagnosed cancer among women in Western countries (International Agency for Research on Cancer, 2000) and the most commonly diagnosed neoplasm among women worldwide (Parkin et al., 1999). There are well characterized roles for reproductive risk factors. Early age at menarche, late age at first birth, having few or no children, short duration of breast feeding and late age at menopause have been found to increase lifetime exposure to circulating

estrogens and predict increased breast cancer risk. (Kelsey, 1993) Many of the established endocrine risk factors for breast cancer are present at high prevalence in industrialized countries, but are associated with only modest relative risks of breast cancer and are largely unmodifiable at the population level (Rockhill et al., 1998).

Other risk factors for breast cancer include: regular alcohol intake; (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Colditz GA et al., 2006) low levels of physical activity and among postmenopausal women, high body mass index (International Agency for Research on Cancer, 2002) and more recently, use of hormone replacement therapy, especially estrogen plus progesterone (IARC Working Group November 2008, report in preparation; personal communication AB Miller, co-chair of the IARC Working Group). The population attributable risk for alcohol and breast cancer in high-income countries has been estimated to be about 4% (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Higher levels of physical activity have been demonstrated to reduce breast cancer risk 25-35% among the tertile or quartile of women who are most active (International Agency for Research on Cancer, 2002). Obesity also increases risk in postmenopausal women resulting in an attributable risk of about 11% (International Agency for Research on Cancer, 2002).

The breast cancer genes, *BRCA1* and *BRCA2* are associated with extremely high relative risks for breast cancer with cumulative lifetime risk of breast cancer of 55-85% up to 70 years of age (Meijers-Heijboer et al., 2001). However, they have a low attributable risk, accounting for only about 3-5% of all breast cancers (Mann et al., 2006; Colditz GA et al., 2006). The frequency of carriers for the *BRCA1* and *BRCA2* genes has been difficult to estimate because of gene size, identification of more than a hundred mutations, and the lack of appropriate assays (Struewing et al., 1997).

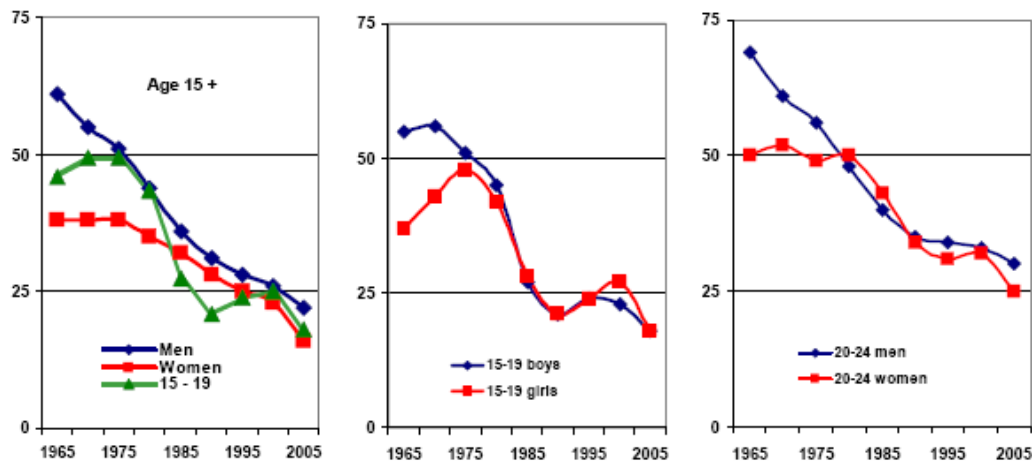
Several lines of evidence suggest that environmental factors can influence breast cancer risk: 1) several fold differences in risk between low-risk and high-risk regions internationally, 2) higher risks in the more industrialized nations, and 3) changes in risks observed over time and in migrant studies (Terry and Rohan, 2002).

4. Active Smoking and Secondhand Smoke Exposure Epidemic in North America in the 20th Century

Concern about exposure of women to tobacco smoke stems from the epidemic of exposure of men and women to tobacco smoke as passive and active smokers over much of the 20th century. Men in many Western countries started smoking in large numbers during the first half of the century and women began to smoke in large numbers in the 1950s and 1960s. In Canada's first national survey of smoking habits in 1965, 61% of men and 38% of women age 15 and over reported being smokers. This included 69% of men and 50% of women aged 20-24, and 69% of men and 48% of women aged 25-44. Fifty-five percent of males and 37% females between the ages of 15 and 19 years old reported being smokers (see Figure 1) (Physicians for a Smoke-Free Canada, 2008).

Smoking in Canada

Figure 1: Smoking in Canada, 1965-2007

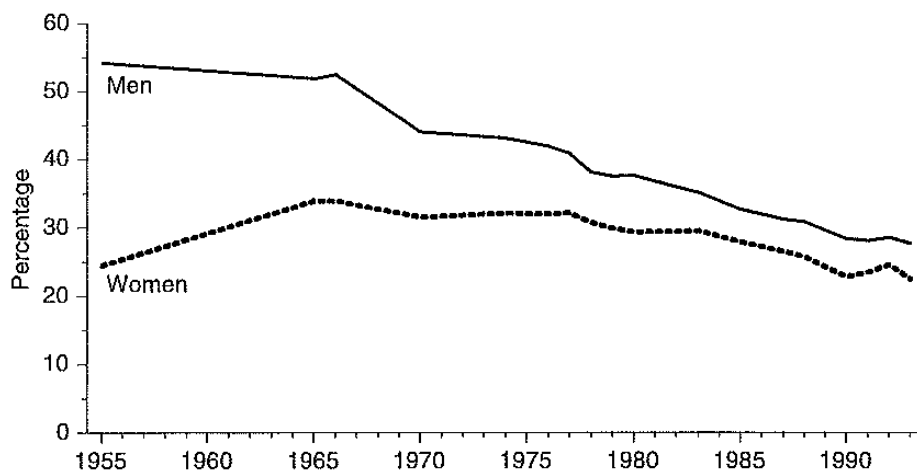


Source: Physicians for a Smoke-Free Canada, 2008

Smoking in U.S.

In the U.S. the smoking pattern was similar with smoking prevalence peaking in the 1950s for men and in the 1960s for women. U.S. National Health Interview Survey NHIS data from 1965 indicated that smoking prevalence was 52% among men and 34% among women (Centers for Disease Control and Prevention, 2007). Fifty-four percent of men and 38% of women aged 18-24 reported smoking in 1965. The large decline in male smoking rates and more gradual decline in women's smoking rates since 1965 in the U.S. are demonstrated in Figure 2.

Figure 2: Percentage of Adults Age ≥ 18 Years Who Are Current Cigarette Smokers,^a by Sex – United States, 1955-1993



^a Estimates since 1992 incorporated some-day smoking

Note: Current Population Survey, 1955; National Health Interview Surveys, 1965-1993

Source: Husten et al., 1996

SHS exposure was largely unrestricted until the 1980s, other than for safety reasons, e.g., around flammable solvents or in theatres; there were virtually no restrictions on where people could smoke. In the mid 1980s workplaces such as hospitals started to voluntarily initiate smoke-free policies, along with some cities and towns. By the 1990s several states passed smoke-free regulations; province and territory-wide bans in Canada have been legislated since the year 2000. As of mid-2008, 12 of 13 Canadian provinces and territories and 25 U.S. states and at least 11 countries have 100% smoke-free public places, including bars and restaurants (Canadian Cancer Society et al., 2009).

5. Differing Toxicities of Mainstream Smoke, Sidestream Smoke and Secondhand Smoke

Mainstream smoke is the smoke directly inhaled through the cigarette by the smoker. Sidestream smoke is the smoke produced by an idling cigarette. Secondhand smoke is the combination of sidestream smoke, exhaled smoke and aged smoke. While the overall individual chemical composition of mainstream, sidestream and SHS differ, each contains many of the same chemical compounds, but in different amounts. There are more than 170 toxic substances in tobacco smoke, including 33 hazardous air pollutants, 47 chemicals restricted as hazardous waste, 67 known human or animal carcinogens, and 3 U.S. EPA criteria pollutants (Repace, 2006). Given that most of tobacco smoke is not inhaled by the smoker, the highest amounts of the common chemicals are found in sidestream smoke. For example, Table 1 provides a comparison between mainstream and sidestream concentrations of eight chemicals and tar. The data presented have been generated by smoking cigarettes under standard smoking machine conditions, collecting both mainstream and sidestream smoke, and analyzing the collected smoke.

Table 1: Ratios of Some Toxic Chemicals and Carcinogens in Undiluted Sidestream Smoke vs Mainstream Smoke

Example	Ratio in Sidestream to Mainstream Smoke
Carbon monoxide	2.5-15 times as much
Nitrogen Oxides	3.7-12.8 times
Nicotine	1.3-21 times as much
Benzene	8-10 times as much
Formaldehyde	50 times as much
NNK	1-22 times as much
Benz(a)pyrene	2.5-20 times as much
Nickel	13-30 times as much
Tar	1.1-15.7 times as much

Source: Hoffman and Hecht, 1989

Sidestream smoke is significantly more toxic than mainstream smoke in laboratory studies. Inhalation studies, conducted at Philip Morris Co. laboratories using male Sprague Dawley rats, demonstrated that sidestream smoke is three to four times more toxic (Schick and Glantz, 2005). Moreover, the toxicity of sidestream smoke appears to increase over time. Later Philip Morris

inhalation studies compared freshly generated sidestream smoke to sidestream smoke that had been aged for 30-90 minutes in a 30m³ chamber. When the smoke doses were equalized on the basis of particulate material concentration, aged sidestream smoke was four times more toxic in 21 day exposures and two times more toxic in 90 day exposures (Schick and Glantz, 2006). Chemical analyses of aging sidestream smoke have also shown that the carcinogenic nitrosamine, NNK, can form from nicotine (Schick and Glantz, 2006).

6. Active Smoking and Secondhand Smoke Cause Other Cancers and Chronic Diseases

That active smoking could be a cause of breast cancer is bolstered by its wide ranging impacts on health in general and the variety of cancers for which smoking has been established as a cause. Smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general (Centers for Disease Control and Prevention, 2008). The International Agency for Research on Cancer has identified smoking as a cause of 15 types of cancer: lung, larynx, oral cavity, pharynx, oesophagus (squamous cell carcinoma), pancreas, urinary bladder and renal pelvis (International Agency for Research on Cancer, 1986); nasal cavities and nasal sinuses, oesophagus, stomach, liver, kidney and uterine cervix as well as myeloid leukaemia (International Agency for Research on Cancer, 2004).

Exposure to SHS causes premature death and disease in children and in adults who do not smoke (California Environmental Protection Agency, 2005; U.S. Department of Health and Human Services, 2006). Exposure of adults to SHS has immediate adverse effects on the cardiovascular system and causes coronary heart disease and lung cancer (California Environmental Protection Agency, 2005; U.S. Department of Health and Human Services, 2006).

About half of long-term smokers will die as a result of their smoking (World Health Organization, 1999). In Canada an estimated 37,209 tobacco-attributable deaths per year are related to passive and active smoking, 23,766 deaths among males and 13,443 among females (Rehm et al., 2006). The adverse health effects from cigarette smoking account for an estimated 438,000 deaths in the United States, or nearly 1 of every 5 deaths each year (Centers for Disease Control and Prevention, 2002).

7. Toxicology and Breast Cancer

There are at least 20 known or suspected human carcinogens identified by IARC that are present in tobacco smoke and that have been demonstrated to induce mammary tumours in rodents (Table 2). Animal studies demonstrate that mammary tumours in rats, mice and/or hamsters can be induced by carcinogens including polycyclic aromatic hydrocarbons, the nitrosamines N-nitrosodiethylamine and N-nitroso-di-n-butyl-amine, the aliphatic compounds acrylonitrile, 1,3-butadiene, urethane and vinyl chloride, and the arylamines 4-aminobiphenyl and ortho-toluidine (International Agency for Research on Cancer, 1986; Office of Research and Development, 2002; National Toxicology Program, 2002). Hecht (2002) and Miller et al. (2007) discuss the current

knowledge and understanding of uptake, metabolism and possible mode of action of a number of these potential human breast carcinogens. The main difference between Hecht (2002) and Miller (2007) is that the latter was primarily concerned with SHS. Neither review could be considered comprehensive on this topic as both target specific issues within the overall subject area, about which there is an extensive amount of literature.

Table 2: Mammary Carcinogens Present in Environmental Tobacco Smoke

Compound	Cigarette Mainstream Smoke (Amount per Cigarette) ^a	Cigarette Sidestream Smoke (Amount per Cigarette) ^b	Cigarette Smoke-Polluted Environments ^c	IARC Class	Mammary gland tumors: Affected Species ^e
Aromatic Hydrocarbons					
Benzene	28 - 106 µg	71 - 134 µg	5 - 22 µg/m ³	1	Mouse
Benzo[a]pyrene	5.6 - 41.5 ng	52 - 95 ng	0 - 3.6 ng/m ³	2A	Rat
Dibenzo[a,h]anthracene	4 ng	^f		2A	Mouse ^g
Dibenzo[a,e]pyrene	Present			2B	Rat ^h
Dibenzo[a,h]pyrene	Present			2B	Rat ^a
Dibenzo[a,i]pyrene	1.7 - 3.2 ng			2B	Rat ^a
Dibenzo[a,l]pyrene	Present			2B	Rat ^a
Nitrosamines					
N-Nitrosodiethylamine	0 - 25 ng		Up to 8.6 ng/m ³	2A	Rat
N-Nitrosodi- <i>n</i> -butylamine	0 - 3.0 ng			2B	Mouse
Aliphatic Compounds					
Acrylamide	Present			2A	Rat
Acrylonitrile	8 - 39 µg	24 - 44 µg		2B	Rat
1,3-Butadiene	24 - 123 µg	81 - 135 µg	19 µg/m ³	2A	Mouse, rat
Isoprene	288 - 1193 µg	743 - 1163 µg	83 - 150 µg/m ³	2B	Rat ⁱ
Nitromethane	0.5 - 0.6 µg			2B	Rat ^j
Propylene oxide	0 - 100 ng			2B	Rat
Urethane	20 - 38 ng			2B	Mouse, hamster
Vinyl chloride	11 - 15 ng			1	Rat, mouse, hamster
Arylamines and Nitroarenes					
4-Aminobiphenyl	2 - 8 ng	21 - 32 ng		1	Rats
Nitrobenzene	25 µg			2B	Mice ^k
<i>ortho</i> -Toluidine	30 - 200 ng			2A	Rats

^a (IARC, 2004) Table 1.10 (the 1999 Massachusetts Benchmark Study)

^b (IARC, 2004) citing Table 1.3 (the 1999 Massachusetts Benchmark Study)

^c (IARC, 2004) citing mainly Jenkins et al., 2000

^d IARC classification: 1 = carcinogenic to humans; 2A = probably carcinogenic to humans; 2B = possibly carcinogenic to humans

^e NTP: 10th Annual Report on Carcinogens (U.S. Department of Health and Human Services, 2002)

^f Blank cell = no data available

^g (IARC, 1973)

^h (Cavalieri et al., 1989; Cavalieri et al., 1991)

ⁱ (IARC, 2000)

^j (IARC, 1994)

^k (IARC, 1996)

8. Biological Mechanisms

There are persuasive biological reasons to suspect that exposure to the carcinogens in tobacco smoke may lead to breast cancer. These biological mechanisms include those summarized by Morabia (2002) as well as from more recent articles. Morabia's summary is updated and extended here:

1. Tobacco smoke contains over a dozen fat-soluble compounds that are known to induce mammary tumours in rodents (Phillips DH et al., 2001); see Table 2. These include several polycyclic aromatic hydrocarbons (PAHs: e.g., benzo[a]pyrene [BP]), heterocyclic amines (such as 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine [PhIP] and 2-amino-3-methylimidazo [4,5-*f*] quinoline [IQ]), aromatic amines (e.g., 4-aminobiphenyl), and nitro-PAHs (including 1-nitropyrene, 4-nitropyrene, 1,6-dinitropyrene). All of these compounds are carcinogenic by a genotoxic mechanism.
2. These carcinogens can be activated into electrophilic intermediates by enzymes active in the human breast epithelial cell. CYP1A1 and CYP1B1 (and possibly very small quantities of CYP1A2) are present either in human breast epithelial cells (HBECs), in breast neutrophils, or in the breast lipids (Phillips DH et al., 2001).
3. Several carcinogenic components of tobacco smoke are known to reach the breast and are secreted into the breast milk. Somogyi and Beck (1993) cite a report identifying PAHs, while Thompson et al. (2002) report finding mutagenic arylamines in human breast milk. LaVoie et al. (1987) report transfer of the tobacco-specific carcinogen, "NNK" and benzo[a]pyrene into the milk of lactating rats. Breast milk extracts have a genotoxic effect on HBECs (Martin et al., 2001).
4. Genes coding for activation/detoxification enzymes such as *NAT2*, *NAT1*, and *CYP1A1*, have been reported to modify the relation of tobacco smoke to breast cancer risk, even though these interactions were not widely reproduced. Of the many possible interactions between genetic polymorphisms for xenobiotic metabolizing enzymes, smoking, and breast cancer, the role of *NAT2* variants has been most intensively investigated. The N-acetylation of carcinogenic aromatic amines is usually a detoxication reaction, catalyzed by the enzyme *NAT2*. A slow acetylator phenotype for *NAT2* (which may result from any of several genetic polymorphisms in the *NAT2* gene) is associated with increased bladder cancer risk from these chemicals: it is hypothesized that this is because for such individuals, the carcinogens will persist longer in the body and may even be activated to more toxic metabolites via another metabolic pathway. However, the effects of the many possible combinations of genetic polymorphisms and chemicals at different dose levels is complex. Phenotypic differences in enzyme levels resulting from different polymorphisms may protect from some carcinogens while enhancing the carcinogenic effect of others, and effects may also vary between tumor sites.

In 1996, Ambrosone et al. reported that postmenopausal women who smoke and who have the slow acetylator *NAT2* had an excess risk of breast cancer occurrence relative to all never-active-smokers (Ambrosone et al., 1996). Two subsequent studies (Hunter et al., 1997; Millikan et al., 1998) of similar design did not reproduce these findings. Two more studies, which included measurement of SHS, found postmenopausal fast acetylators to be at higher risk of breast cancer if they were exposed to SHS (Morabia et al., 2001; Chang-Claude et al., 2002). Morabia (2002) suggested that this implicated heterocyclic amines (e.g., PhIP) rather than PAHs (e.g., BP) as the relevant tobacco carcinogens. Ambrosone et al. (2008) were unable in their meta-analysis to demonstrate clear associations between *NAT2* status and breast cancer among ever active smokers, but did find a clear dose-response relationship between breast cancer and active smoking among slow acetylators. Ambrosone et al. (2008) pointed out that the broad designations of slow vs fast acetylator phenotype encompass a range of different genetic polymorphisms of this gene, which may have different metabolic capabilities with respect to different carcinogens. Since tobacco smoke contains both bicyclic aromatic amines, which are detoxified by the fast acetylator *NAT2*, and heterocyclic amines, which are not, the polymorphisms of other enzymes may play important roles as well.

5. Electrophilic metabolites of tobacco compounds bind to DNA and form DNA adducts that can be detected in HBECs and in both normal and cancerous breast tissue biopsies from women who are current or former smokers or who are passively exposed to tobacco smoke (Firozi et al., 2002; Perera et al., 1995; Li et al., 1996; Faraglia et al., 2003) as reviewed by OEHHA (2005), Miller et al. (2007) and Hecht (2002).
6. Genomic alterations observed in vitro after exposure of HBECs to tobacco carcinogens resemble those seen in familial breast cancer (Russo, 2002). Microsatellite instability has been detected in HBECs transformed with chemical carcinogens in *loci* flanking the breast cancer susceptibility gene *BRCA2* (13q12-13). Loss of heterozygosity in chromosome 17p13, which may indicate deletion of the remaining normal allele of a tumour-suppressor gene, was observed in immortalized HBECs treated with benzo[a]pyrene.

On the other hand, in a competing fashion, cigarette smoke may also act to reduce breast cancer risk through two mechanisms. There is some indication that cigarette smoke may exert an antiestrogenic effect (Chen et al., 2005), as women who smoke have an earlier menopause, thus fewer years of menstruation, and cigarette smoking alters estrogen metabolism (MacMahon et al., 1982; Michnovicz et al., 1986). Antiestrogenic effects of smoking may override potential carcinogenic effects and associations may be noted only among women who are less capable of detoxifying tobacco smoke carcinogens (Ambrosone and Shields, 1997). As well, cigarette smoking is inversely related to obesity (Albanes et al., 1987), which could help to prevent the effect of obesity in increasing breast cancer risk in postmenopausal women (International Agency for Research on Cancer, 2002).

9. Epidemiological Studies of Active Smoking and Breast Cancer

Active smoking has been examined as a possible risk factor for breast cancer for some time. Palmer and Rosenberg (1993) identified 47 studies of breast cancer and smoking published from 1960 through 1992. Among those, 10 case-control and five cohort studies published between 1984 and 1992 met their quality criteria for inclusion. Their review concluded that there was “little evidence to suggest that cigarette smoking materially increases risk. Most studies have found no association or very small positive associations for ever smoking, current smoking, or heavy smoking” (Palmer and Rosenberg, 1993).

The next major review of smoking and breast cancer, by Terry and Rohan (2002) cited 67 additional studies of breast cancer and smoking published since the Palmer and Rosenberg review. Terry and Rohan (2002) identified four areas where findings were suggestive of an increased breast cancer risk but more research was required; 1) smoking of long duration, 2) smoking before the first full term pregnancy, 3) SHS, as well as 4) increased risk among women of certain genotypes who smoke.

Since that review, at least 40 more original studies, 6 meta-analyses and 3 major reports have been published, many helping clarify the relationships identified by Terry and Rohan (2002). Appendix 1 presents summaries of 16 epidemiologic reviews of breast cancer and tobacco smoke between 1993 and 2008. Included among these are 7 reviews and 4 meta-analyses that address active smoking, 5 reviews and 4 meta-analyses of SHS, and 3 meta-analyses of genetics and active smoking.

In this section we first revisit a meta-analysis published in 2002, then look in turn at the first two active smoking issues identified by Terry and Rohan (2002), long duration smoking as evaluated by years of smoking and pack-years and smoking before first full-term pregnancy and the associated issue of age at smoking initiation.

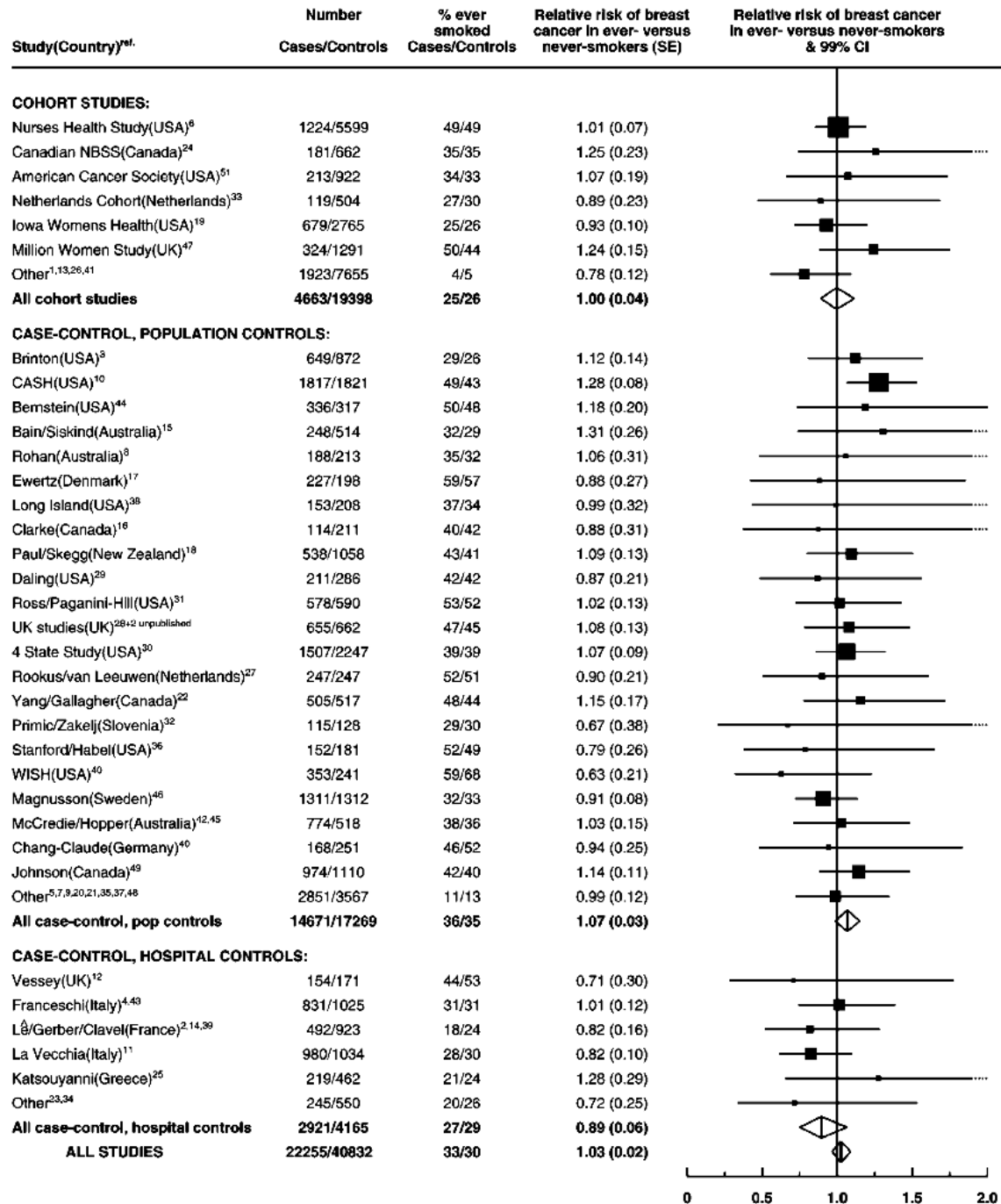
9.1 Collaborative Group on Hormonal Factors in Breast Cancer - Meta-analysis of Smoking, Alcohol and Breast Cancer, 2002

The Collaborative Group on Hormonal Factors in Breast Cancer meta-analysis of Smoking, Alcohol and Breast Cancer (2002) was highlighted in both the Surgeon General’s (U.S. Department of Health and Human Services, 2004; U.S. Department of Health and Human Services, 2006) and IARC’s (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2004) evaluations of active and passive smoking and breast cancer.

The Collaborative Group analysis (2002) involved individual data from 53 studies of breast cancer, estimated by the authors to be 80% of the world literature on the subject at the time. The authors reported a 7.1% increase in breast cancer risk for every 10 grams of alcohol per day (10 grams of alcohol \approx 1 drink). Regarding tobacco, they concluded that “the relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. When analyses were restricted to 22,255 women with breast cancer and 40,832 controls who reported drinking no alcohol, smoking was not associated with breast cancer (compared to never-smokers, relative risk for ever-smokers=1.03; 95% CI 0.98–1.07, and for current smokers=0.99; 0.92–1.05. The results for alcohol

and for tobacco did not vary substantially across studies, study designs, or according to 15 personal characteristics of the women; nor were the findings materially confounded by any of these factors.” An abstract of the study is included in Appendix 1 (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). The key tobacco analysis, a comparison of breast cancer risk for ever vs never smokers among women who reported they drank no alcohol, is summarized in Figure 3.

Figure 3: Breast Cancer Risk for Ever vs Never Smokers Among Women Who Reported Drinking No Alcohol



Source: From the Collaborative Group on Hormonal Factors in Breast Cancer (2002)

Given the limitations of comparing only ever vs never smokers, we compared the ever smoker vs never (active) smoker risk estimates in the Oxford report with risk estimates we were able to find in the literature for longer duration smoking in the same studies. Table 3 compares the ever smoker vs never (active) smoker risk reported in the Oxford meta-analysis for never drinkers, with risks reported for the longest duration of smoking in the combined group of drinkers and non-drinkers for the same studies. Given the concern about confounding by alcohol, we excluded 4 case-control studies where longer duration smoking risks had been published but did not control for alcohol. Higher breast cancer risk is generally observed for the active smokers in each study with longest smoking duration compared to ever smokers. For case-control studies, a lower risk is observed among long-term smokers in one study (> 0.1 reduction), essentially the same risk is seen in 4 studies (risk difference -0.1 to 0.1) and higher risks are observed in 5 studies (risk difference >0.1), although only one is statistically significant. Three of the 4 cohort studies, each controlled for alcohol, have statistically significant risk increases for longer smoking duration, with risks of 1.18 (95% CI 1.00-1.38), 1.38 (1.05-1.38) and 1.50 (1.19-1.89). The fourth shows no elevated risk for ≥ 40 yrs of smoking (1.05 (0.90-1.21)).

Table 3: Comparison of Breast Cancer Risks: Oxford 2002 Ever vs Never (Active) Smoker Risk vs Longest Duration Risk Where Alcohol Was Controlled

2002 OXFORD – Tobacco Consumption (Ever vs Never) and Breast Cancer Risk				Reports on Smoking Duration and Breast Cancer Risk		
Oxford Studies (Country)	First Author, Year of Publication	Study Group	Risk Estimate	First Author, Year of Publication	Longest Duration	Relative Risk with 95% CI
Cohort Studies						
Nurses' Health Study (USA)	Willett, 1987	Nurses' Health Study	1.01	Egan et al. (Egan et al., 2002)	≥40 years	1.05 (0.90-1.21)
Canadian NBSS (Canada)	Friedenreich, 1993	Canadian National Breast Cancer Study	1.25	Cui et al. (2006)	≥40 years	1.50 (1.19-1.89)
American Cancer Society (U.S.)	Calle 1994	Cancer Prevention II Study	1.03	Calle et al. (1994)	≥40 years	1.38 (1.05-1.38)
Iowa Women's Health (U.S.)	Gapstur, 1992	Iowa's Women Health Study	0.93	Olson et al. (2005)	≥40 years	1.18 (1.00-1.38)
Population-based Case-control Studies						
Bernstein (USA)	Enger, 1999	University of Southern California Cancer Surveillance Program (CSP)	1.18	Prescott et al. (2007)	≥20 years	1.12 (0.79-1.59)
Rohan (Australia)	Rohan, 1988	Adelaide, South Australia	1.06	Rohan & Baron (1989)	500+ cig-years	1.57 (0.99-2.48)
Clarke (Canada)	Rosenberg, 1990	Princess Margaret Hospital, Toronto, Ontario	0.88	Palmer et al. (1991)	≥22 years	1.7 (0.9-3.3) U.S. 1.0 (0.8-2.1) Can
Ross/Paganini-Hill (U.S.)	Longnecker, 1995	Cancer Surveillance Program (Los Angeles County, SEER)	1.02	Prescott et al. (2007)	>20 years	1.12 (0.79-1.59)
UK studies (UK)	Smith, 1994 + 2 unpublished	UKCCSG	1.08	Smith et al. (1994)	>10 years	0.97 (0.76-1.24)
4 State studies (USA)	Longnecker, 1995	Collaborative Breast Cancer Study (CBCS)	1.07	Baron et al. (1996)	>50 years	1.07 (0.84-1.37)
Stanford/Habel (USA)	Rossing, 1996	Cancer Surveillance Program (King County, Washington State, SEER)	0.79	Alberg et al. (2004)	>15 to ≤ 82.5 pkyrs ^a	1.7 (0.70, 4.2)
Magnusson (Sweden)	Magnusson, 1999	6 Swedish Cancer Registries	0.91	Magnusson et al. (2007)	>30 years	1.1 (0.9-1.2) current 0.9 (0.7-1.4) past
Chang-Claude (Germany)	Kropp 2002	2 regions in southern Germany, "Rhein-Neckar-Odenwald" and "Freiburg	1.15	Kropp & Chang-Claude (Kropp and Chang-Claude, 2002)	≥20 years	1.45 (0.96-2.19)
Johnson (Canada)	Johnson, 2000	Canadian National Enhanced Cancer Surveillance System	1.14	Johnson et al. (2000)	≥21 years	1.7 (1.1-2.7) postmenopausal 2.1 (0.9-4.7) premenopausal

^a pkyrs = pack-years

9.2 Active Smoking Duration and Pack-Years

Terry and Rohan, 2002

Terry and Rohan (2002) reviewed active smoking risk but went beyond the Oxford meta-analysis by also evaluating the duration and intensity of smoking. For both case-control and cohort studies increases in risk were often observed (see Tables 4 and 5, replicated from the Terry and Rohan report). For higher intensity smoking risk estimates were above 1.0 for 12 of 15 cases-control studies and 8 of 11 cohort studies. For longer duration of smoking risk estimates were above 1.0 for 8 of 12 cases-control studies and for the three cohort studies which reported on duration.

Cohort Studies of Smoking and Breast Cancer

Since Terry and Rohan's (2002) synthesis, a number of newer studies, particularly cohort studies, have also observed increased risk associated with long duration and/or high pack-years of smoking (Reynolds et al., 2004; Gram et al., 2005; Olson et al., 2005; Cui et al., 2006). The Panel considered 11 studies of 10 cohorts that have examined duration and/or pack-years of smoking and breast cancer as providing key evidence. They are briefly summarized below. Smoking duration and pack-year results are then summarized for case-control and cohort studies in text and Tables 6 and 9.

Calle et al. (1993) This prospective cohort study (Cancer Prevention Study II) followed 604,412 American women for six years from interview in 1982. The results of this study are not included with the other cohort studies in the tables or evaluation because this was the only cohort to use fatal breast cancer as opposed to incident breast cancer as an endpoint. Breast cancer mortality was less than unity for former smokers (RR 0.85 (95% CI 0.70-1.03)), but increased breast cancer mortality was observed for current smokers (RR 1.26 (95% CI 1.05-1.50)). Breast cancer mortality for current smokers increased with increasing number of cigarettes per day and total number of years smoked. The RR was 1.74 (95% CI 1.15-2.62) for current smokers of 40 or more cigarettes per day.

Hunter et al. (1997) Using the Nurses' Health Study cohort, women who gave a blood specimen in 1989-1990 were followed. Invasive breast cancer was diagnosed in 466 women, who were then matched to 466 controls in a nested case-control study to evaluate NAT2 acetylator genotype and smoking. Thirty or more pack-years of smoking was associated with a RR of 1.3 (95% CI 0.9-1.9). Among slow acetylators, current smokers had a RR of 1.4 (95% CI 0.7-2.6) compared with nonsmoking rapid acetylators. If the comparisons had been to never-smoking slow acetylators, the risk estimates would have been increased by a factor of 1.25, suggesting a risk estimate of 1.9 for slow acetylators among current smokers smoking 15+ cigarettes per day (Morabia, 1998).

Table 4: Population-based Case-control Studies of Cigarette Smoking and Breast Cancer Risk

First author, study year	Years of data collection	No. of cases/ controls	Age range (yrs)	Smoking frequency (cigarettes/day)		Smoking duration (yrs)		Pack-years (packs/day × years)		Age smoking commenced (yrs)	
				Comparison	OR (95% CI) ^a	Comparison	OR (95% CI)	Comparison	OR (95% CI)	Comparison	OR (95% CI)
Marcus, 2000 (64)	1993–1996	864/790	20–74	20+ vs. never	1.1 (0.9–1.4)	20+ vs. never	1.3 (1.1–1.8)			<15 vs. never	1.5 (0.9–2.5)
Millikan, 1998 (66)	1993–1995	498/473	20–74	>20 vs. never	1.1 (0.7–1.7)	20+ vs. never	1.6 (1.1–2.3)				
Morabia, 1996 (67)	1992–1993	244/1032	30–74	20+ vs. never	4.6 (2.2–9.7)			20+ vs. never	2.9 (1.4–6.0)		
Gammon, 1998 (56) ^b	1990–1992	1645/1497	<45	>20 vs. never	1.0 (0.7–1.4)	>21 vs. never	0.7 (0.5–0.9)	>20 vs. never	0.8 (0.6–1.1)	≤15 vs. never	0.6 (0.4–0.9)
Baron, 1996 (47)	1988–1991	6888/9529	<75	>40 vs. never	1.1 (0.8–1.5)	50+ vs. never	1.1 (0.8–1.4)			≤15 vs. never	1.0 (0.8–1.3)
Lash, 1999 (61)	1983–1986	266/765	<50–80	20+ vs. never	1.6 (0.6–4.3)	40+ vs. never	2.4 (1.1–5.5)			<17 vs. never	2.4 (0.8–7.2)
Adami, 1988 (183)	1984–1985	422/527	<45	20+ vs. never	1.1 (0.7–1.8)	20+ vs. never	1.2 (0.8–1.7)			<15 vs. never	1.3 (0.7–2.5)
Palmer, 1991 (175)	1982–1986	607/1214	35–69	25–34 vs. never	1.5 (0.9–2.5)	40+ vs. never ^c	1.0 (0.5–2.1)			<14 vs. never	1.9 (0.9–4.4)
Ewertz, 1993, 1990 (94, 189)	1983–1984	623/578	25–69	20+ vs. never	0.8 (0.6–1.0)	30+ vs. never	1.0 (0.7–1.5)			<15 vs. never	0.9 (0.4–1.8)
Smith, 1994 (73)	1982–1985	755/755	<36	16+ vs. never	1.1 (0.8–1.5)	10+ vs. never	1.0 (0.8–1.2)	10+ vs. never	1.0 (0.8–1.4)	<16 vs. never	1.1 (0.8–1.4)
Rohan, 1989 (185)	1982–1984	451/451	20–74	>15 vs. never	1.6 (1.0–2.6)			25+ vs. never	1.6 (1.0–2.5)		
Field, 1992 (184)	1982–1984	1617/1617	20–79	>40 vs. never	1.2 (0.7–2.0)	40+ vs. never	1.2 (0.7–2.0)	40+ vs. never	1.1 (0.8–1.4)	<20 vs. never	1.0 (0.9–1.2)
Mayberry, 1994 (90)	1980–1982	148/167	20–54					11+ vs. none	1.1 (0.6–1.9)		
Chu, 1990 (188)	1980–1982	4720/4682	20–54	25+ vs. never	1.2 (1.1–1.4)	30+ vs. never	1.1 (0.9–1.3)	40+ vs. never	1.1 (0.9–1.4)	<17 vs. never	1.1 (1.0–1.2)
O'Connell, 1987 (186)	1977–1978	276/1519		>20 vs. never	0.6 (0.3–1.1)						
Stroup, 1987 (187) ^d	1959–1960	4720/4682	20–54	25+ vs. never	1.2 (1.0–1.4)	30+ vs. never	1.1 (1.0–1.3)			<15 vs. never	1.1 (0.9–1.4)

^a OR, odds ratio; CI, confidence interval.

^b Results presented are for current smokers. Results for former smokers showed statistically non-significant positive associations with smoking.

^c The analysis was limited to smokers of 25 or more cigarettes/day.

^d Results presented are for current smokers. Results for former smokers were similar.

Source: Terry and Rohan (2002)

Table 5: Prospective Cohort Studies of Cigarette Smoking and Breast Cancer Risk

First author, study year	Years of data collection	No. of cases/no. in cohort	Age range (yrs)	Smoking frequency (cigarettes/day)		Smoking duration (yrs)		Pack-years (packs/day × years)		Age smoking commenced (yrs)	
				Comparison	RR (95% CI) ^a	Comparison	RR (95% CI)	Comparison	RR (95% CI)	Comparison	RR (95% CI)
Zheng, 1999 (76)	1986	273/657	55–69	15+ vs. none ^b	1.1 (0.7–1.6)						
Calle, 1994 (51) ^c	1982–1986	800/604412	30–70+	40+ vs. never	1.7 (1.2–2.6)	40+ vs. never	1.4 (1.1–1.8)			<16 vs. never	1.6 (1.2–2.2)
Terry, 2002 (195)	1980–1985	2552/89835	40–59	40+ vs. never	1.3 (1.1–1.7)	40+ vs. never	1.6 (1.2–2.2)	40+ vs. never	1.4 (1.2–1.6)	<16 vs. never	1.1 (0.9–1.4)
Egan, 2002 (84)	1982	3140/78206	36–61			40+ vs. never	1.1 (0.9–1.2)			<17 vs. never	1.2 (1.0–1.4)
Manjer, 2001 (63)	1974–1992	268/10902	25–75	20+ vs. never	1.3 (1.0–1.8)						
Vatten, 1990 (196)	1974–1978	242/24329	35–51	10+ vs. none	0.9 (0.6–1.2)						
Hiatt, 1988 (194)	1979–1984	303/68674		40+ vs. never	1.2 (0.5–2.8)						
Hunter, 1997 (58)	1976	466/466 ^d	30–55	15+ vs. never ^e	1.6 (1.0–2.4)			30+ vs. never	1.3 (0.9–1.9)		
London, 1989 (192)	1976	1788/117557	30–55	25+ vs. never	1.0 (0.9–1.2)					<17 vs. never	1.1 (0.9–1.3)
Hiatt, 1986 (193)	1964–1972	1363/84172	20–84	“heavy” vs. never	1.2 (0.9–1.6)						
Schatzkin, 1989 (191)	1949–1988	143/2636	31–64	20+ vs. none	1.0 (0.6–1.7)						
Nordlund, 1997 (79)	1963	170/26000	18–69	16+ vs. never	1.1 (0.7–1.7)					<19 vs. never	1.2 (0.8–1.8)

^a RR, relative risk; CI, confidence interval.

^b Results presented are for smokers of 25 years or longer.

^c The endpoint examined was breast cancer mortality.

^d This study was of nested case-control design (the numbers represent cases/controls).

^e Results presented are for smoking 10 years prior to diagnosis (results for smoking at interview were essentially the same).

Source: Terry and Rohan (2002)

Egan et al. (2002) This analysis of the Nurse's Health Study, a largely Caucasian population, included 78,206 women followed prospectively from 1982 until June 1996, reporting 3,140 cases of invasive breast cancer. The RR for breast cancer was 1.04 (95% CI 0.94-1.15) for current smoking and 1.09 (95% CI 1.00-1.18) for ex-smokers. The relative risk was higher among ex-smokers who recently quit smoking (adjusted RR 1.17 (95% CI 1.01-1.40)) compared to never-smokers. If women exposed to SHS were excluded from the unexposed category, then the relative risks for current and past active smoking increased slightly (adjusted RR 1.15 (95% CI 0.98-1.34) and 1.17 (95% CI 1.01-1.34), respectively).

Terry et al. (2002) A prospective Canadian cohort study involved 89,835 women enrolled within a multi-center, randomized trial of mammography screening. Women age 40-59 were recruited from the general population between 1980 and 1985 and followed initially through December 1993. Breast cancer cases (n = 1,306) were ascertained through linkages with a population-based cancer database and national vital statistics. The adjusted RR for breast cancer for current smoking was statistically significant (RR 1.14 (95% CI 1.03-1.27)), relative to all never-smokers. Breast cancer risk increased with duration of smoking; women smoking over 40 years had a statistically elevated risk (RR 1.61 (95% CI 1.19-2.19)), with a significant p for trend of 0.003. The risk for women smoking > 20 cigarettes per day for over 40 years was 1.83 (95% CI 1.29-2.61).

Al-Delaimy et al (2004) This study utilized the Nurses' Health Study II cohort and followed 112,844 women aged 25-42 years in 1989 for 10 years. Among the 1,009 incident breast cancer cases, smoking was related most strongly to the risk of estrogen receptor-positive breast cancers. For women who had smoked for ≥ 20 years, the RR of estrogen receptor-positive cancer was 1.37 (95% CI 1.07-1.74), for estrogen receptor-negative cancer 1.04 (95% CI 0.71-1.53). For smoking before age 15, the RRs were 1.49 (95% CI 1.03-2.17) for estrogen receptor-positive cancer and 1.19 (95% CI 0.69-2.08) for estrogen receptor-negative cancer.

Reynolds et al. (2004) A U.S. prospective cohort of professional school employees (the California Teacher Study) followed 116,544 women from 1995 to 2000. Breast cancer was diagnosed in 2,005 women. Current smoking was associated with a significantly elevated risk (Hazard Ratio (HR) of breast cancer in the full cohort regardless of whether passive smokers (residential exposure only) were included (HR 1.32; 95% CI 1.10-1.57), or excluded (HR 1.25; 95% CI 1.02-1.53). This effect was most pronounced in postmenopausal current smokers. An analysis limited to the 35,123 nondrinkers, found that current smokers continued to have a significantly elevated risk of breast cancer (HR 1.66; 95% CI 1.15-2.40), providing evidence to counter concerns that associations between active smoking and breast cancer are actually measuring a surrogate of alcohol exposure.

Hanaoka et al. (2005) examined breast cancer risk in a prospective cohort study of 21,805 middle-aged Japanese women. In 1990, a self administered questionnaire collected baseline data. Cancer incidence and mortality data were collected during follow-up through the end of 1999 and 180 women had developed breast cancer. Ever smokers, who were premenopausal at baseline had a

significantly elevated risk of developing breast cancer (RR 3.9; 95% CI 1.5-9.9), but postmenopausal smokers did not (RR 1.1; 95% CI 0.5-2.5). Similarly, among never-smokers, passive smoking was associated with increased risk for women premenopausal at baseline (RR 2.6; 95% CI 1.3-5.2), but not women who were postmenopausal (RR 0.7; 95% CI 0.4-1.0).

Gram et al. (2005) A large population-based prospective study (The Norwegian-Swedish Cohort) followed 102,098 women ages 30 to 50 years, from 1991 through the year 2000. Incident, invasive breast cancer was diagnosed in 1,240 women. Comparing smokers to never-smokers, they found significantly increased risks for smoking >10 cigarettes/day for 20+ years (RR 1.34; 95% CI 1.06-1.70), initiating smoking prior to first birth (RR 1.27; 95% CI 1.00-1.62), before menarche (RR 1.39; 95% CI 1.03-1.87), or before age 15 years (RR 1.48; 95% CI 1.03-2.13). The increased risks were observed among non-drinkers of alcohol, women with and without family history of breast cancer, premenopausal and postmenopausal women and in both the Norwegian and the Swedish cohort.

Olson et al. (2005) utilized The Iowa Women's Health Study, a prospective study of 41,836 women 55 to 69 years old at baseline in 1986, to examine postmenopausal breast cancer risk associated with cigarette smoking before first pregnancy. Women who began smoking before their first pregnancy had a RR of 1.21 (95% CI 1.07-1.37), whereas women who began smoking after their first full-term pregnancy did not have increased risk (RR of 1.03 (95% CI 0.88-1.37)). Smoking for more than 40 years was associated with a RR of 1.18 (95% CI 1.0-1.4).

Cui et al. (2006) extended the follow-up of the Canadian Cohort (Terry et al. 2002) to an average of 16.1 years and 4,445 incident breast cancer cases. Risk patterns were similar with the longer follow-up: long duration smoking (> 40 years) was associated with a RR of 1.50 (95% CI 1.19-1.89), and >40 pack-years (RR of 1.17 (95% CI 1.02-1.34)). Although both analyses are reported in the tables for completeness, only the longer follow-up was used to summarize the results across studies.

Ha et al. (2007) This nationwide cohort study of 56,042 female U.S. radiologic technologists evaluated 906 incident breast cancer cases (1983-1998). The study found that smoking risk differed by reproductive period: a 3% increase per pack-year of smoking between menarche and first childbirth (RR 1.03 (95% CI 1.02-1.05)); an independent increase in risk with younger age at smoking initiation (age <15 vs nonsmokers 1.48 (95% CI 0.77-2.84), p for trend 0.06); and no effect for smoking after first pregnancy. Ten or more pack-years of smoking before the first full-term pregnancy was associated with a RR of 1.78 (95% CI 1.27-2.49).

Summaries of Risk Associated with Duration and Pack-Years

Table 6 summarizes the cohort studies that have reported on smoking duration and breast cancer risk and Table 7 the case-control studies. Five of the 6 cohort studies report increased risk for the highest duration category of smoking - 2 borderline significance (RR 1.14 (95% CI 1.0-1.3); 1.18 (95% CI 1.0- 1.4)) and 3 statistically significant increases (RR 1.21 (95% CI 1.06-1.45); 1.36 (95% CI

1.1-1.7); and 1.50 (95% CI 1.19-1.89)). Among the case-control studies a number suggested increased risk and some did not.

Results for risk associated with pack-years of smoking are reported in Table 8 for cohort studies and Table 9 for case-control studies. Four of the 6 cohort studies report increases in risk associated with the highest pack-year category, and three reach statistical significance (RR 1.17 (95% CI 1.02-1.34); 1.25 (95% CI 1.06-1.47); 1.46 (95% CI 1.11-1.93)). The only study with a risk estimate below 1.0 was a study from Japan which reported on only 21 women with breast cancer who had ever smoked. For case-control studies the pattern is less consistent with a number of studies suggesting increased risk and a number not.

The Panel noted the consistency of the cohort studies in observing increased risk estimates associated with longer duration and higher pack-years and was more persuaded by these studies than the more inconsistent, case-control literature. In some of the case-control studies, selection bias could hide small increases in risk, if cases who were long-term smokers were slightly less likely to participate in the studies than long-term smokers who were potential controls. This is not a concern in the cohort studies, where subjects are established and smoking habits documented - long before diagnosis.

Table 6: Cohort Studies of Active Smoking and Breast Cancer, Risk by Smoking Duration

Cohort Study (First Author, Year)	Average Years of Follow-up	No. Cases	Duration (Years) ^a	Relative Risk (95% CI) ^b	Adjusted/Matched For
Terry et al. (2002)	10	204	1-9	0.93 (0.80-1.09)	Age in 5-year age groups, treatment allocation (intervention, control), study center, Quetelet's index (quartiles), education level, vigorous physical activity (hr/day in tertiles), OC use (never <4 levels of duration), HRT (never <4 levels of duration), parity (quartiles), age at menarche (quartiles), history of benign breast disease, practice breast self-exam, family history of breast cancer in a first-degree relative, menopausal status and alcohol consumption
		279	10-19	0.97 (0.85-1.11)	
		426	20-29	1.06 (0.94-1.19)	
		268	30-39	1.14 (0.99-1.31)	
		46	≥40	1.61 (1.19-2.19)	
Egan et al. (2002)	14	621	<20	1.04 (0.95-1.15)	Current age (for duration smoked, continuous variable), age at menarche, first birth and parity, history of benign breast disease, family history of breast cancer in a mother/sister, menopausal status and age at menopause, weight at 18 years and adult weight change, adult height, grams of alcohol consumed/week, total carotenoid intake, and menopausal hormone use
		450	20-29	1.11 (1.00-1.24)	
		475	30-39	1.08 (0.97-1.21)	
		235	≥40	1.05 (0.90-1.21)	
Al-Delaimy et al. (2004)	10	Full Study (25-42 years at baseline)			BMI, height oral contraceptives, parity, age at first birth, age at menarche, family history of breast cancer, benign breast cancer, alcohol consumption, and menopausal status
		52	<10	1.14 (0.85-1.52)	
		99	10-14	1.19 (0.96-1.48)	
		96	15-19	1.06 (0.85-1.33)	
Reynolds et al. (2004)	5	Full Study (75% postmenopausal)			Age, race, family history of breast cancer, age at menarche, parity, age at first full-term pregnancy, physical activity, alcohol consumption, BMI, menopausal status interaction, hormone therapy use;
		176	≤10	0.99 (0.85-1.17)	
		193	11-20	1.17 (1.00-1.37)	
		163	21-30	1.17 (0.99-1.38)	
		251	>31	1.15 (1.00-1.33)	
		Premenopausal			
		52	≤10	1.14 (0.85-1.55)	
		33	11-20	1.10 (0.76-1.58)	
		21	21-30	1.06 (0.67-1.66)	
		7	>31	0.99 (0.46-2.13)	
		Postmenopausal			
		101	≤10	0.95 (0.77-1.17)	
140	11-20	1.22 (1.02-1.47)			
113	21-30	1.07 (0.88-1.31)			
230	>31	1.16 (0.99-1.34)			

Table 6: Cohort Studies of Active Smoking and Breast Cancer, Risk by Smoking Duration (cont'd)

Cohort Study (First Author, Year)	Average Years of Follow-up	No. Cases	Duration (Years) ^a	Relative Risk (95% CI) ^b	Adjusted/Matched For
Gram et al. (2005)	9	Full Study 30-50 years at baseline			Age at enrolment, menopausal status, number of children, age at first birth, hormonal contraceptive use, BMI, alcohol consumption
		Current smokers			
		68	1-19	0.93 (0.68-1.28)	
		96	20-24	1.09 (0.81-1.45)	
		196	≥25	1.26 (0.98-1.63)	
		Ever smokers			
158	20-24	1.13 (0.88-1.45)			
234	>=25	1.36 (1.06-1.74)			
Olson et al. (2005)	14	Postmenopausal			Age, education, family history of breast cancer, age at menarche, age at menopause, oral contraceptive use, hormone replacement therapy, BMI, waist-to-hip ratio, height, BMI at 18 years, physical activity, alcohol consumption
		140	1-19	1.01 (0.83-1.21)	
		319	20-39	1.13 (0.99-1.29)	
209	≥40	1.18 (1.00-1.38)			
Cui et al. (2006) (extended follow-up for same cohort as Terry 2002)	16	Full Study (40-59 years at baseline)			Age, randomization group, study center, body mass index, educational level, vigorous physical activity, oral contraceptive use, hormone replacement therapy, parity, age at menarche, history of benign breast disease, practice breast self-exam, family history of breast cancer in a degree relative, menopausal status, alcohol consumption
		362	1-9	1.00 (0.90-1.12)	
		507	10-19	1.02 (0.93-1.13)	
		761	20-29	1.09 (1.00-1.19)	
		453	30-39	1.14 (1.03-1.27)	
77	≥40	1.50 (1.19-1.89)			

^a Highest exposures were selected from each study

^b All relative risks are relative to never active smokers unless indicated otherwise

Table 7: Case-Control Studies of Active Smoking and Breast Cancer - Smoking Duration

First Author, Year	Country	Age Range	Duration (Years) ^a	Premenopausal Odds Ratio ^b (95% CI)	Postmenopausal Odds Ratio ^b (95% CI)	Full Study Odds Ratio ^b (95% CI)	Adjusted/ Matched For
Brinton et al. (1986)	U.S.	DNI	≥40 (current)			1.26 (0.9-1.7)	Age, age at menopause
Stroup et al. (1987)	U.S.	20-54	≥30	1.1 (1-1.3)			Age, age at first birth, parity, Quetelet index, family history of breast cancer, history of benign breast disease, menopausal status, oral contraceptive, hormone replacement use
Adami et al. (1988)	Norway, Sweden	<45	≥20	1.2 (0.8-1.7)			Education, age at menopause, age at first birth, parity, menopausal status, history of benign breast disease, family history of breast cancer, oral contraceptive, alcohol use
Brownson et al. (1988)	U.S.	DNI	≥15	1.79 (0.87-3.65)	0.92 (0.61-1.38)		Age, age at first pregnancy, parity, age (at menarche, at menopause), marital status, family history of breast cancer, contraceptive use, replacement hormone use
Rohan & Baron (1989)	Australia	20-74	>25 years ^c	1.64 (0.71-3.8)	1.57 (0.9-2.76)	1.57 (0.99-2.48)	Family history of breast cancer, practice of self-breast exams, history of benign breast disease, alcohol use
Ewertz (1990)	Denmark	25-69	30-39	0.99 (0.67-1.47)	1.09 (0.8-1.49)	0.99 (0.8-1.23)	Age, residence
Chu et al. (1990)	U.S.	20-54	≥30			1.1 (0.9-1.3)	Age, age at first birth, history of benign breast disease, menopausal status, estrogen use
Palmer et al. (1991)	U.S.	<70	≥40			1.7 (0.9-3.3)	Age, residence, age at menopause, age at menarche, age at first birth, parity, family history of breast cancer, history of benign breast disease, BMI, oral contraceptive use, centre, alcohol use, education
Palmer et al. (1991)	Canada	<70	≥40			1.0 (0.5-2.1)	Birth year, place of residence
Field et al. (1992)	U.S.	20-79	≥40			1.04 (0.84-1.29)	
Pawlega (1992)	Poland	≥35	≥20 ^e	0.5 (0.1-2.3)	1.5 (0.7-3.2)		Age, education, social class, marital status, number of persons in household, BMI, alcohol use (vodka 20 years prior)
Rautalahti et al. (1993)	Finland	35-69	>15	2.95 (1.05-8.31)	1.85 (0.67-5.14)		Age
Smith et al. (1994)	UK	<36	≥10	0.97 (0.76-1.24)			Age (at menarche, at first birth), nulliparity, breast feeding, family history of breast cancer in 1 st degree relatives, history of benign breast disease, alcohol use, oral contraceptives

Table 7: Case-Control Studies of Active Smoking and Breast Cancer - Smoking Duration (cont'd)

First Author, Year	Country	Age Range	Duration (Years) ^a	Premenopausal Odds Ratio ^b (95% CI)	Postmenopausal Odds Ratio ^b (95% CI)	Full Study Odds Ratio ^b (95% CI)	Adjusted/ Matched For
Bennicke et al. (1995)	Denmark	15-92	≥31			1.6 (1.1-2.2)	Age, parity, family history of breast cancer, breast feeding
Baron et al. (1996)	U.S.	<74	>30, ≤40	1.28 (0.88-1.85)	1.09 (0.96-1.23)	1.12 (1-1.25)	Age (at menarche, at first birth), parity, lactation history, history of benign breast disease, alcohol use, menopausal status
Braga et al. (1996)	Italy	20-74	≥30			0.99 (0.8-1.2)	Age, centre, education, parity, menopausal status, age (at menopause, at menarche), history of benign breast disease, family history of breast cancer, BMI, oral contraceptives
Millikan et al. (1998)	U.S.	20-74	>20	1.4 (0.8-2.6)	1.7 (1.1-2.6)	1.6 (1.1-2.3)	Age, place of residence, age (at menarche, at first birth), parity, family history of breast cancer, history of benign breast disease, alcohol use
Gammon et al. (1998)	U.S.	<45	>21	0.7 (0.52-0.94)			Age, centre, alcohol use, parity, age (at first birth, at menarche), breast feeding, abortion, miscarriage, ever married, menopausal status, BMI, household income, oral contraceptive use, caloric intake, hormone use, history of benign breast disease, place of residence, family history of breast cancer
Lash & Aschengrau (1999)	U.S.	≤80	≥40		2.4 (1.1-5.5)		Age, parity, history of radiation therapy, BMI, history of breast cancer in 1st degree relative, history of breast cancer, history of benign breast disease
Johnson et al. (2000)	Canada	25-74	≥21 ^d	2.1 (0.9-4.7)	1.7 (1.1-2.7)		Age, age (at menarche, at end of 1st pregnancy) province, height, BMI, education, alcohol use, physical activity, number of live births, months of breastfeeding
Delfino et al. (2000)	U.S.	≥40	>26 ^d			0.74 (0.34-1.61)	Age, menopausal status, history of breast cancer in 1st/2nd degree relatives
Band et al. (2002)	Canada	<75	≥20 (nulliparous)	2.27 (0.72-7.13)	1.39 (0.61-3.17)		Age, age (at menarche, at menopause), ethnic origin, marital status, education, family history of breast cancer in 1st degree relative, history of benign breast disease, weight, BMI, oral contraceptive use, hormone replacement use, reproductive history, breastfeeding, alcohol
Band et al. (2002)	Canada	<75	≥20 (parous)	1.5 (0.98-2.28)	0.98 (0.76-1.25)		
Kropp & Chang-Claude (2002)	Germany	≤50	≥20 ^d	1.45 (0.96-2.19)			Menopausal status, number of months breast feeding, education, history of breast cancer in 1st degree relatives, BMI, alcohol use

Table 7: Case-Control Studies of Active Smoking and Breast Cancer - Smoking Duration (cont'd)

First Author, Year	Country	Age Range	Duration (Years) ^a	Premenopausal Odds Ratio ^b (95% CI)	Postmenopausal Odds Ratio ^b (95% CI)	Full Study Odds Ratio ^b (95% CI)	Adjusted/ Matched For
Lash & Aschengrau (2002)	U.S.	DNI	>40 ^d			0.9 (0.8-1)	History of medical radiation therapy, BMI, family history of breast cancer, history of malignant /benign breast cancer, alcohol, parity
Zheng et al. (2002)	U.S.	30-80	>30	1.2 ^e (0.3-5.4)	1.4 (0.9-2.2)	1.3 (0.8-2)	Age, age at first birth, number of months breastfeeding, BMI, family history of breast cancer
van der Hel et al. (2003)	Netherlands	20-59	≥30			1.55 (0.94-2.54)	Age, age (at menarche, at first birth), menopausal status, place of residence
Mechanic et al. (2006)	U.S.	21-74	>20 ^d			1.1 (0.9-1.5)	Age, parity, family history of breast cancer, obesity, alcohol use
Lissowska et al. (2006)	Poland	20-74	>20	2.33 (1.32-4.13)	0.78 (0.61-0.99)	0.99 (0.83-1.20)	Age, age (at menarche, at first birth, at menopause), site, education, number of children, history of screening mammography, hormone replacement therapy, smoking intensity, history of benign breast disease, family history of breast cancer, oral contraceptives
Prescott et al. (2007)	U.S.	20-49	>20	1.12 (0.79-1.59)			Age, age (at menarche, at first birth), place of residence, education, parity, family history of breast cancer, alcohol
Magnusson et al. (2007)	Sweden	50-74	>30		1.1 (0.9-1.2)		Age, age at first birth, BMI, alcohol
Rollison et al. (2008)	U.S.	40-79	≥40 ^d		1.35 (0.55-3.32)		Age, menopausal status, education

^a Highest exposures were selected from each study

^b All odds ratios are relative to never smokers unless indicated otherwise

^c Based on 500 cigarette-years with 20 cigarettes per pack

^d Reference group comprises never active or passive smokers

^e Cases for analysis <10 (low statistical power)

Table 8: Cohort Studies of Active Smoking and Breast Cancer, Risk by Pack-Years

Cohort Study (First Author, Year)	Name of Study, No. Subjects	No. Cases	Smoking Categories	Relative Risk^a (95% CI)	Adjusted/ Matched For
Hunter et al. (1997) USA 1989-1994	Nurses' Health Study		Pack-years^b (Combined NAT2)		Age (at menarche, at first birth), parity, BMI, family history of breast cancer in mother or sister, history of benign breast cancer
		110	0-19	1.2 (0.9-1.7)	
		55	20-29	1.8 (1.1-3.0)	
		101	≥30	1.3 (0.9-1.9)	
Goodman et al. (1997) Japan 1979-1989	Life Span Study (LSS) 22,000 women	21	Ever smoker	0.78 (0.49-1.24)	Attained age, age at the time of the bombings, city, radiation dose to the breast
		19	Current smoker	0.97 (0.60-1.58)	
		2	Former smoker	0.32 (0.08-1.28)	
		9	Pack-years		
		8	<10	1.41 (0.71-2.76)	
		8	≥10	0.52 (0.25-1.06)	
Terry et al. (2002) Canada 1980-1993	Canadian National Breast Screening Study (NBSS) 89,807 women	DNR	Current smoker	1.14 (1.03-1.27)	Age in 5-year age groups, treatment allocation, study center, Quetelet's index, education level, vigorous physical activity, OC use, parity, age at menarche, history of benign breast disease, practice breast self-exam, family history of breast cancer in 1st-degree relative, menopausal status, alcohol
		DNR	Former smoker	0.99 (0.90-1.09)	
			Pack-years		
		396	1-9	0.98 (0.87-1.10)	
		251	10-19	0.97 (0.85-1.12)	
		204	20-29	1.08 (0.93-1.25)	
		191	30-39	1.21 (1.04-1.42)	
		151	≥40	1.37 (1.15-1.62)	
		152	1-9 yrs + <20 cpd ^c	0.92 (0.77-1.09)	
		41	1-9 yrs + ≥20 cpd	0.99 (0.72-1.33)	
11	<40 yrs + ≥20 cpd	1.17 (0.64-2.21)			
35	≥40 yrs + ≥20 cpd	1.83 (1.29-2.61)			
Reynolds et al. (2004) U.S.	California Teachers' Study 116,544 women		Pack-years		Age, age (at menarche, at first full-term pregnancy), race, parity, family history of breast cancer, physical activity, BMI, menopausal status, BMI and menopausal status interaction, hormone therapy use, alcohol
		338	≤10	1.02 (0.91-1.16)	
		164	11-20	1.24 (1.05-1.46)	
		94	21-30	1.12 (0.91-1.39)	
173	≥31	1.25 (1.06-1.47)			
Gram et al. (2005) Norway & Sweden 1991-2000	Norwegian-Swedish Cohort Study 102,098 women		Pack-years		Age at enrolment, menopausal status, number of children, age at first birth, contraceptive use, BMI, alcohol
			Current smoker		
		162	0-14	0.95 (0.74-1.20)	
		90	15-19	1.28 (0.96-1.72)	
		108	≥20	1.48 (1.14-1.96)	
			Pack-years		
			Ever smoker		
153	0-14	1.01 (0.85-1.40)			
114	15-19	1.35 (1.02-1.77)			
125	≥20	1.46 (1.11-1.93)			

Table 8: Cohort Studies of Active Smoking and Breast Cancer, Risk by Pack-Years (cont'd)

Cohort Study (First Author, Year)	Name of Study, No. Subjects	No. Cases	Smoking Categories	Relative Risk ^a (95% CI)	Adjusted/ Matched For	
Olson et al. (2005) U.S. 1989-1999	Iowa Women's Health Study (IWHS) 37,105 women	266	Current smoker	1.19 (1.03-1.37)	Age, education family history of breast cancer, age at menarche, age at menopause, oral contraceptive use, hormone replacement therapy, BMI, waist-to-hip ratio, height, body mass index at the age of 18 years, physical activity, alcohol	
			Pack-years			
			1-19	1.05 (0.91-1.21)		
			20-39	1.18 (1.02-1.37)		
		167	≥40	1.15 (0.96-1.37)		
Cui et al. (2006) Canada (1980-1996) (extended the follow-up for same cohort as Terry 2002)	Canadian National Breast Screening Study (NBSS) 89,835 women	N/A N/A 728 466 388 332 246	Current smoker	1.18 (1.09-1.27)	Age (at baseline, at menarche), randomization group, study centre, BMI, educational level, vigorous physical activity, OC use, hormone replacement therapy, parity, history of benign breast disease, practice breast self-exam, family history of breast cancer, menopausal status, alcohol	
			Former smoker	1.00 (0.93-1.08)		
			Pack-years			
			1-9	1.02 (0.93-1.11)		
			10-19	1.02 (0.92-1.13)		
			20-29	1.13 (1.02-1.27)		
30-39	1.21 (1.07-1.36)					
		246	≥40	1.17 (1.02-1.34)		

^a All relative risks are relative to never (active) smokers unless indicated otherwise

^b Relative risk relative to never (active) smoking, NAT2 rapid genotype

^c Cpd = cigarettes per day

Table 9: Case-Control Studies of Active Smoking and Breast Cancer -Smoking Pack-years

First Author, Year	Country	Age Range	Duration (Years) ^a	Premenopausal Odds Ratio ^b (95% CI)	Postmenopausal Odds Ratio ^b (95% CI)	Full Study Odds Ratio ^b (95% CI)	Adjusted/ Matched For
Baron et al. (1984)	U.S.	40-89	>16			0.93 (0.76-1.13)	Age, marital status, number of children, Quartelet Index
Schechter et al. (1985)	Canada	40-59	>20	3.5 (1.3-9.9)	1.4 (0.7-2.9)	2.0 (1.1-3.4)	Age, age (at menarche, at first birth, parity, at menopause), family history of breast cancer, history of benign breast disease, ethnicity, breast symptoms, menstrual irregularity, marital status, centre, estrogen replacement use, oral contraceptives, education, height, history of breast self-exams, number of previous mammograms
Rohan & Baron (1989)	Australia	20-74	>26		1.57 (0.9-2.76)	1.57 (0.99-2.48)	Family history of breast cancer, practice of self-breast exams, history of benign breast disease, alcohol
Schechter et al. ^c (1989)	U.S.	40-59	>25	1.0 (0.5-2.3)	1.4 (0.9-2.2)	1.3 (0.9-1.9)	Age, age (at menarche, at first birth, at menopause), parity, family history of breast cancer, history of benign breast disease, ethnicity, breast symptoms, menstrual irregularity, marital status, estrogen replacement use, oral contraceptive use, education, height, history of breast self-exams, number of previous mammograms, centre
Ewertz (1990)	Denmark	25-69	>26			0.91 (0.69-1.18)	Age, place of residence
Chu et al. (1990)	U.S.	20-54	>41	1.5 (1-2.3)	1 (0.7-1.6)	1.1 (0.9-1.4)	Age, age at first birth, history of benign breast disease, menopausal status, estrogen use
Field et al. (1992)	U.S.	20-79	>41			1.05 (0.81-1.35)	Birth year, place of residence
Smith et al. (1994)	UK	<36	>11	1.02 (0.76-1.37)			Age (at menarche, at first birth), nulliparity, breast feeding, family history of breast cancer in 1 st degree relatives, oral contraceptive use, history of benign breast disease, alcohol
Mayberry et al. (1994)	U.S.	20-54	11-15			1.1 (0.6-1.9)	N/A
Morabia et al. (1996)	Switzerland	30-74	>21 ^d			3.2 (1.8-5.9)	Age, age (at menarche, at first birth), education, BMI, oral contraceptive use, family history of breast cancer, history of benign breast disease

Table 9: Case-Control Studies of Active Smoking and Breast Cancer -Smoking Pack-years (cont'd)

First Author, Year	Country	Age Range	Duration (Years) ^a	Premenopausal Odds Ratio ^b (95% CI)	Postmenopausal Odds Ratio ^b (95% CI)	Full Study Odds Ratio ^b (95% CI)	Adjusted/ Matched For
Gammon et al. (1998)	U.S.	<45	>20	0.84 (0.62-1.12)			Age, age (at first birth, at menarche), centre, parity, breast feeding, abortion, BMI, miscarriage, marital and menopausal status, household income, oral contraceptives, hormone use, caloric intake, history of benign breast disease and family breast cancer, place of residence, alcohol
Johnson et al. (2000)	Canada	25-74	>30 ^d	1.5 (0.4-5.9)	1.6 (1-2.6)		Age, age (at menarche, at end of 1st pregnancy), province, height, BMI, physical activity, education, number of live births, months of breastfeeding, alcohol
Band et al. (2002)	Canada	<75	>21 Nulliparous	7.48 (1.59-35.2)	1.08 (0.46-2.50)		Age at menarche and menopause, ethnic origin, marital status, education, family history of breast cancer in 1st degree relative, history of benign breast disease, weight, BMI, oral contraceptive use, hormone replacement use, reproductive history, breastfeeding, alcohol
Band et al. (2002)	Canada	<75	>21 Ever Pregnant	1.46 (0.92-2.32)	1.02 (0.78-1.35)		Menopausal status, number of months breast feeding, education, history of breast cancer in 1st degree relatives, BMI, alcohol
Kropp & Chang-Claude (2002)	Germany	<51	>22 ^d	1.13 (0.68-1.88)			Age, BMI, age at first birth, number of months breastfeeding, family history of breast cancer
Zheng et al. (2002)	U.S.	30-80	>20	0.4 ^e (0.1-1.4)	1.2 (0.7-1.9)	1 (0.6-1.5)	Age, menopausal status
Alberg et al. (2004)	U.S.	N/A	>15			1.7 (0.7-4.2)	Age, history of benign breast disease, BMI, family history of breast cancer, history of fertile problems, number of children, menopausal status, weight
Gammon et al. (2004)	U.S.	24-98	>21 ^d			1.33 (0.97-1.83)	Age, age (at menarche, at first birth), number of children, history of benign breast disease, family history of breast cancer, waist-hip-ratio, alcohol
Metsola et al. (2005)	Finland	37-91	>6 ^d			1.08 (0.72-1.62)	Age, age at menarche, number of children, history of benign breast disease, family history of breast cancer, alcohol
Sillanpaa et al. (2005)	Finland	N/A	>6 ^d			1.23 (0.8-1.9)	Age, site, education, age at (menarche, first birth and menopause), oral contraceptives, number of children, screening, hormone replacement therapy, history of benign breast disease, family breast cancer
Lissowska et al. (2006)	Poland	20-74	>10	2.44 (1.47-4.05)			

Table 9: Case-Control Studies of Active Smoking and Breast Cancer -Smoking Pack-years (cont'd)

First Author, Year	Country	Age Range	Duration (Years) ^a	Premenopausal Odds Ratio ^b (95% CI)	Postmenopausal Odds Ratio ^b (95% CI)	Full Study Odds Ratio ^b (95% CI)	Adjusted/ Matched For
Magnusson et al (2007)	Sweden	50-74	>30		0.9 (0.7-1.2)		Age, age at first birth, BMI, alcohol
Suzuki et al. (2007)	Japan	20-79	>30 no familial breast cancer ^f			0.97 (0.72-1.31)	Age, BMI, physical activity, referral pattern to their hospital, alcohol
Suzuki et al. (2007)	Japan	20-79	>30 familial breast cancer ^g			4.33 (1.65- 11.40)	Age, BMI, physical activity, referral pattern to their hospital, alcohol
Slattery et al. (2008)	U.S.	25-79	>15 NHW ^h	1.6 (1.1-2.4)	1 (0.8-1.2)		Age, parity, centre, BMI, aspirin/NSAIDs, long-term physical activity, recent estrogen in postmenopausal women long-term alcohol use
Slattery et al. (2008)	U.S.	25-79	>15 HAI ⁱ	0.9 (0.5-1.7)	1.2 (0.8-1.7)		
Rollison et al. (2008)	U.S.	40-79	>31 ^d		1.03 (0.43-2.49)		Age, menopausal status, education

^a Highest exposures were selected from each study

^b All relative risks are relative to never active smokers unless indicated otherwise

^c Pack-years based on 500 cigarette-years

^d Reference group comprises never active or passive smokers

^e Cases for analysis <10 (low statistical power)

^f Women who have no 1st degree relative with breast cancer

^g Women who have a 1st degree relative with breast cancer

^h NHW = Non-Hispanic Whites

ⁱ HAI = Hispanic American Indian

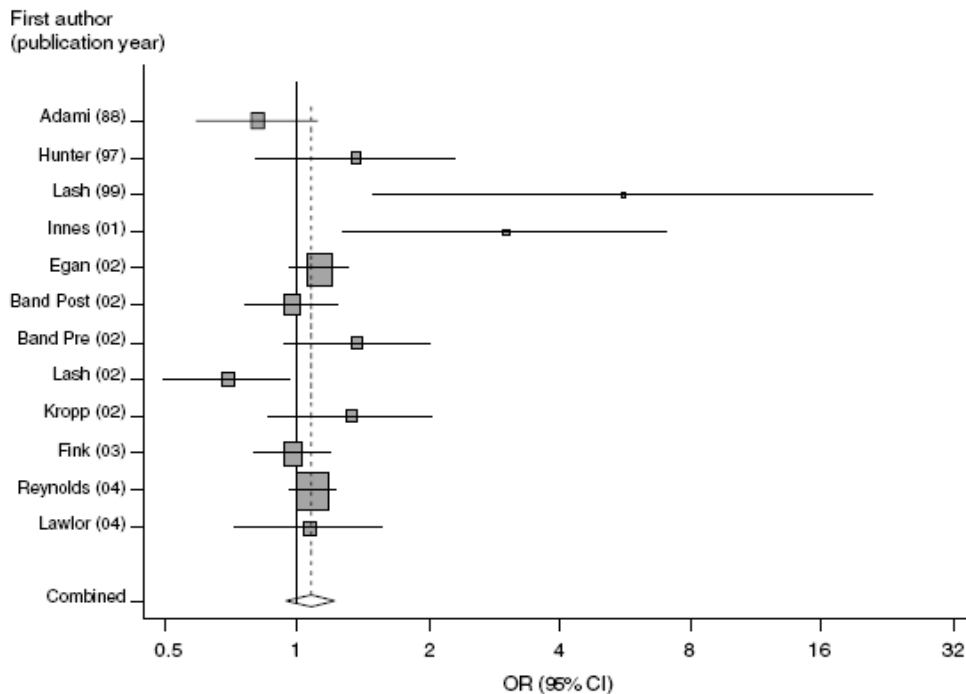
We return to the examination of duration and intensity of active smoking in Section 10 in the context of genetics.

9.3 Cigarette Smoking Before a First Full-term Pregnancy

The relation of tobacco smoke exposure to risk of breast cancer may depend on a woman’s parity or age at the time of exposure. Breast epithelial cells do not become fully differentiated until after a first full-term pregnancy. Thus, the period between the onset of puberty and first full-term pregnancy may be a time of higher risk of cancer initiation (Russo and Russo, 1980; Russo and Russo, 1993). In addition, adolescence, a time of rapid cell proliferation, may be a critical period of risk, as evidenced by studies of atomic bomb survivors and women medically exposed to ionizing radiation at young ages (Kelsey, 1993). Palmer et al. (1991) hypothesized that women who begin smoking in the early teenage years may have an increased risk of breast cancer. Since that time, numerous case-control and cohort studies have examined breast cancer risk in relation to age at commencement of smoking and in relation to the timing of exposure with regard to first full-term pregnancy.

Lawlor et al. (2004) performed a meta-analysis of 12 studies of smoking and breast cancer that had examined smoking before first pregnancy. The meta-analysis resulted in a summary risk estimate of 1.07 (95% CI 0.94 -1.22) and led the authors to conclude that there was no relationship between smoking before/during first pregnancy and breast cancer (summarized in Figure 4).

Figure 4: Meta-analysis of Studies Assessing the Effect of Smoking Before/During First Pregnancy with Breast Cancer Risk



Source: From Lawlor et al. 2004

Since the Lawlor meta-analysis, at least 11 more studies, including four cohort studies, have been published which are informative. A summary of the studies to date with data on these topics is presented in Tables 10a for case-control studies and 10b for cohort studies.

In Tables 10 and 11, 11 studies provide evidence of no association of breast cancer risk with smoking before a first full-term pregnancy and 13 provide evidence of a positive association of the magnitude of 1.1-1.4 for any smoking before the first full term pregnancy. All 8 cohort studies had risk estimates greater than 1.0, two of the estimates were statistically significantly increased and three were close to statistical significance. The null studies include two (Morabia et al., 1996; Lash and Aschengrau, 2002) that reported elevated relative risk estimates for that exposure category but equally large estimates for smoking that began after the first full-term pregnancy. The null studies include four smaller studies (Lash and Aschengrau, 2002; Fink and Lash, 2003; Lawlor et al., 2004; Rollison et al., 2008) and only one that was relatively large (Magnusson et al., 2007). The studies with positive findings were generally larger than the null studies including four of the cohort studies which included several-thousand cases (Egan et al., 2002; Reynolds et al., 2004; Gram et al., 2005; Cui et al., 2006). One of the studies included in Table 10 (Innes and Byers, 2001) assessed smoking while pregnant and yielded a relative risk estimate of 3.0 (1.3-7.2) for this exposure. Band et al. (2002) analyzed pre- and postmenopausal women separately and found a positive association of smoking before first pregnancy in premenopausal women but not postmenopausal women; Slattery et al. (2008) analyzed non-Hispanic women and Hispanic women separately in their study of women in the south-western U.S. and observed a positive association among non-Hispanic women but no association among Hispanic women.

Overall, taking into account the relative sizes of the studies and the magnitude of the associations observed, the available data suggest that active smoking before a first full-term pregnancy may be associated with an increase in risk of breast cancer. There was not a consistent pattern of findings with regard to breast cancer among pre- and postmenopausal women.

Table 10: Case-control Studies Reporting Results on Age at Initiation of Cigarette Smoking in Relation to Breast Cancer Risk

First Author, Year	Any Before	Duration	Relative Risk (95% CI)
Adami et al. (1988)	X		0.81 (0.6-1.1)
Morabia et al. (1996)	X		3.0 (1.7-7.0)
Lash and Aschengrau (1999)	X		1.1 (0.6-2.0)
Innes and Byers (2001)		During pregnancy	3.0 (1.3-7.2)
Band et al. (2002) (postmenopausal)	X		0.97 (0.76-1.24)
Lash and Aschengrau (2002)	X		0.69 (0.50-0.96)
Band (2002) (premenopausal)	X		1.37 (0.93-2.0)
Kropp and Chang-Claude (2002)	X		1.32 (0.86-2.0)
Fink and Lash (2003)		During pregnancy	1.0 (0.81-1.2)
Li et al. (2005)	X		1.3 (1.0-1.7)
Lissowska et al. (2006)	X		1.14 (0.98-1.32)
Magnusson et al. (2007)	X		1.1 (ns)
Prescott et al. (2007)		>10 yrs	1.03 (0.75-1.43)
Slattery et al. (2008) (Hispanic and Native American)	X		1.0 (0.8-1.3)
Slattery et al. (2008) (Non-Hispanic White)	X		1.4 (1.0-1.9)
Rollison et al. (2008)	X		1.06 (0.5-2.4)

Table 11: Cohort Studies Reporting Results for Cigarette Smoking Before First Full-term Pregnancy in Relation to Breast Cancer Risk by Year

First Author, Year	Any Before	Duration	Relative Risk (95% CI)
Egan et al. (2002)		5+ yrs	1.13 (0.99-1.30)
Al-Delaimy et al. (2004)		20+ yrs ^a	1.10 (0.80-1.52)
Lawlor et al. (2004)	X		1.06 (0.72-1.56)
Reynolds et al. (2004)		5+ yrs	1.13 (1.00-1.28)
Gram et al. (2005)	X		1.27 (1.00-1.62)
Olson et al. (2005)	X		1.21 (1.07-1.37)
Cui et al. (2006)		5+ yrs	1.13 (1.01-1.25)
Ha et al. (2007)		10+ pack-yrs	1.39 (0.82-2.35)

^a For Al-Delaimy, 2004, 15-19 years of smoking before first pregnancy was associated with a RR of 1.42 (95% CI 1.10-1.83)

9.4 Age at Initiation of Smoking

With regard to age at initiation of smoking, 14 studies provide no evidence of an association and 14 studies show evidence of a positive association of smoking at a young age with breast cancer risk (Tables 12 and 13). Study results were judged to show no evidence of an association if the relative risk estimate for the lowest category of age started smoking relative to no smoking was 1.1 or lower and not statistically significant, if estimates for the oldest age started smoking were as high or higher than the estimate for the youngest age started (Chu et al., 1990; Lash and Aschengrau, 2002; Johnson et al., 2000; Olson et al., 2005; Rollison et al., 2008). With a few exceptions, the positive studies were larger than the null studies and were more likely to include women in the birth cohorts for which smoking during the teenage years was common. All seven cohort studies had risk estimates between 1.1 and 1.5 and three reached statistical significance. The highest risks among the cohort studies were observed for studies reporting on young women categorized as starting to smoke before age 15, although the evidence is more mixed for the case-control studies. The weight of evidence from these studies provides support for the hypothesis that initiation of smoking during the early teenage years increases risk of breast cancer. As with smoking before a first full-term pregnancy, some of the positive studies included premenopausal women only, postmenopausal women only, or both.

Table 12: Case-control Studies Reporting Results on Age at Initiation of Cigarette Smoking in Relation to Breast Cancer Risk

First Author, Year	Earliest Age Started	Relative Risk (95% CI)
Brinton et al. (1986)	<17	1.3 (1.0-1.6)
Stroup et al. (1987)	<15	1.1 (0.9-1.4)
Adami et al. (1988)	<15	1.3 (0.7-2.5)
Ewertz (1990)	<15	0.87 (0.42-1.77)
Chu et al. (1990)	<17	1.1 (1.0-1.2)
Palmer et al. (1991)	<16	1.8 (1.0-3.4)
Palmer et al. (1991)	<16	1.7 (1.0-2.9)
Field et al. (1992)	<15	1.15 (0.51-2.61)
Smith et al. (1994)	<15	1.1 (0.8-1.4)
Braga et al. (1996)	<16	0.97 (0.7-1.3)
Baron et al. (1996)	<15	1.17 (0.96-1.43)
Gammon et al. (1998)	<16	0.6 (0.4-0.9)
Lash and Aschengrau (1999)	<17	2.4 (0.8-7.2)
Marcus et al. (2000)	<15	1.5 (0.9-2.5)
Johnson et al. (2000)	<16 (premenopausal)	2.1 (1.0-4.3)
	<16 (postmenopausal)	1.2 (0.7-1.9)
Kropp and Chang-Claude (2002)	<16	1.02 (0.62-1.68)
Lissowska et al. (2006)	<17	1.07 (0.80-1.42)
Magnusson et al. (2007)	<20	1.2 (1.0-1.4)
Prescott et al. (2007)	<16	0.83 (0.59-1.16)
Slattery et al. (2008)	<17	1.3 (0.9-1.9)
Rollison et al. (2008)	<17	1.3 (1.0-1.6)

Table 13: Cohort Studies Reporting Results on Age at Initiation of Cigarette Smoking in Relation to Breast Cancer Risk

First Author, Year	Earliest Age Started	Relative Risk (95% CI)
Egan et al. (2002)	<17	1.19 (1.03-1.37)
Al-Delaimy et al. (2004)	<15	1.29 (0.97-1.71)
Reynolds et al. (2004)	<20	1.17 (1.05-1.30)
Gram et al. (2005)	<15	1.48 (1.03-2.13)
Olson et al. (2005)	<19	1.12 (0.92-1.36)
Cui et al. (2006)	<16	1.11 (0.97-1.28)
Ha et al. (2007)	<15	1.48 (0.77-2.84)

There is likely to be considerable overlap between women who began smoking at a young age and women who smoked for five or more years before their first full term pregnancy. Most studies have not had the power to disentangle these closely related exposures. Egan et al. (2002) addressed this issue in the Nurses' Health Study in which data on 3,140 incident cases of invasive breast cancer were analyzed. Both early age at initiation of smoking and smoking before a first full-term pregnancy were associated with an increased risk of breast cancer. The largest risk with smoking before a first full-term pregnancy occurred among those women who began smoking by 16 years, suggesting that early smoking per se may increase risk.

10. Epidemiologic Studies of Active Smoking and Genetics

Inherited genetic predispositions are important risk factors for the development of cancers in general (Suzuki et al., 2007). In this section we review recent literature that has examined the impact of smoking on breast cancer risk among potentially genetically susceptible subgroups of women defined in three different ways. We begin with recent research on smoking among cohorts of women who were carriers of mutations in *BRCA1* and *BRCA2*. Next we review smoking related risk among women defined by having a family history of breast cancer. Finally we then turn to three recent meta-analyses that summarize the epidemiologic research on smoking, genotype and breast cancer, with a focus on the *NAT2* polymorphism, evaluated in the most depth in the meta-analysis and pooled analysis of Ambrosone et al. (2008). All three approaches yield results that suggest smoking increases risk among genetically susceptible subgroups of women.

10.1 Smoking and *BRCA1* and *BRCA2*

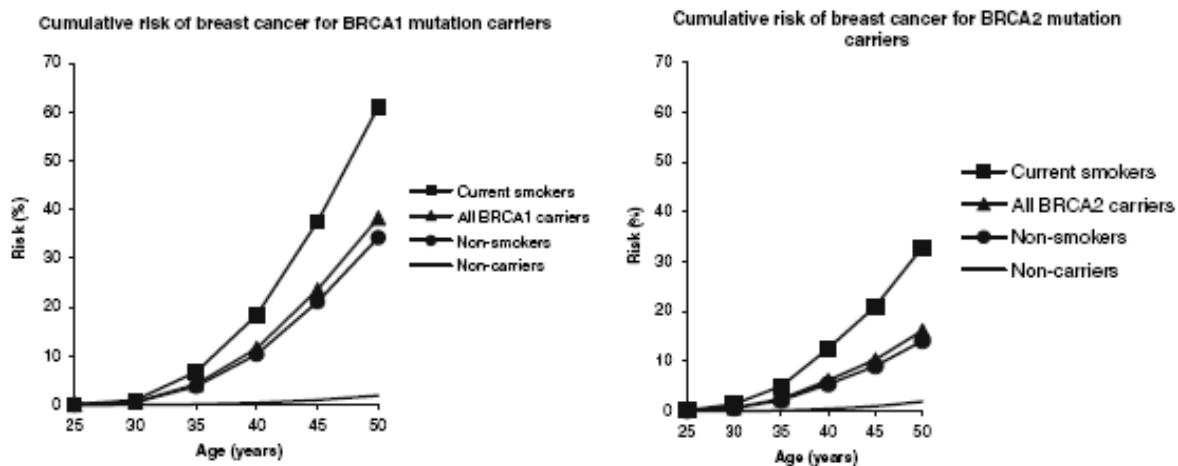
In a recent report on collaboration among familial breast cancer registries in the United States, Australasia, and the Ontario Cancer Genetics Network, a case-control study of women under 50 who were carriers of mutations in *BRCA1* and *BRCA2* reported increased risk of breast cancer associated with as little as five pack-years of smoking (Breast Cancer Family Registry et al., 2008). Compared to non-active smokers, the risk associated with five or more pack-years of smoking was 2.3 (95% CI

1.6–3.5) for *BRCA1* carriers and 2.6 (1.8–3.9) for *BRCA2* carriers. In both groups, risk increased 7% per pack-year ($p < 0.001$).

The results differed from five previous studies examining *BRCA* carriers that had not found an increased risk associated with smoking (Brunet et al., 1998; Colilla et al., 2006; Nkondjock et al., 2006; Ghadirian et al., 2004; Gronwald et al., 2006); the first two studies noted a significant inverse association. However, the authors of the most recent study argued that because the other studies had used prevalent cases, many of which had been diagnosed many years before study (3 of the studies had an average interval of at least 8 years between diagnosis and testing or interview), the results could have been biased towards the null or even towards a protective effect. It is known that smokers have reduced survival because of deaths from other causes associated with smoking. As a result, a disproportionate number of smokers with breast cancer would have died, making them unavailable for study and possibly creating the appearance that smoking was equally or less common in cases than controls carrying one of the breast cancer genes. The recent study included prevalent cases as well, but the average time from diagnosis to interview was only 2 years and none of the cases had been diagnosed more than 5 years before the study.

The impact of this smoking risk is presented in Figure 5 below, reproduced here from the original report. The results suggest that in this study population those women who were *BRCA1* carriers and smoked would have had a roughly 60% chance of developing breast cancer by age 50, but only a 35% chance if they had not smoked. Similarly for women who were *BRCA2* carriers, about 35% of smokers and only 15% of never-(active) smokers would have developed breast cancer by age 50.

Figure 5: Estimated Cumulative Risk of Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers to Age 50



Source: Breast Cancer Family Registry et al. (2008)

Motivated by the 2007 collaborative case-control study, researchers reanalyzed the earlier Ghadirian et al., (2004) study (Ginsburg et al., 2009). They did not find increased risk for smokers vs never smokers among the 764 case-control pairs of women with *BRCA1* or *BRCA2* that had been

interviewed within 2 years of diagnosis, but for this subset of their dataset the authors presented risks only for ever vs never smoking and no dose-response results. *BRCA1* carriers who were past-smokers had an increased risk (OR 1.27; 95% CI 1.06-1.50).

The provocative results of the recent international study (Breast Cancer Family Registry et al., 2008) will need to be replicated before judgement can be made; if they are replicated, they will provide strong evidence in support of the conclusion that there are subgroups of women who are genetically more sensitive to tobacco smoke.

10.2 Smoking, Familial History of Breast Cancer and Breast Cancer Risk

Suzuki et al. (2007) A recent study from Japan (Suzuki et al., 2007) adds further evidence suggesting that the smoking risk related to breast cancer is among genetically susceptible subgroups. The effect of familial history of cancer and smoking on common cancer risks was examined in this case-control study of 18,836 incident cancer cases (3,861 breast cancer cases) and 28,125 age and sex matched controls aged 20 to 79 collected between 1988 and 2004. Breast cancer was the only cancer among 12 cancer sites studied, where a significant interaction between smoking history and a family history of breast cancer in first degree relatives at the same cancer site was observed (interaction $p = 0.01$).

For women who smoked but who had no familial history of breast cancer in first degree relatives (mother or sister), no increases in risk were observed for either low or high pack-years of smoking (see Table 14). On the other hand having a mother or sister with breast cancer was associated with a 44% increase in breast cancer risk among women who never smoked, one to 30 pack-years of smoking was associated with a doubling of risk and more than 30 pack-years of smoking with a four-fold increase.

Table 14: Association Between Smoking History and Risk of Breast Cancer by Family History of Breast Cancer in First Degree Relatives (Sisters or Mother)

Smoking Pack-Years	No family history of breast cancer in first degree relatives Odds Ratio (95% CI)	Family history of breast cancer in first degree relatives Odds Ratio (95% CI)
Never active smoker	1.00 (Referent)	1.44 (1.21-1.71)
Smoker (<=30 Pack-Years)	0.98 (0.87-1.10)	1.95 (1.36 – 2.81)
Smoker (>30 Pack-Years)	0.97 (0.720-1.31)	4.33 (1.65- 11.40)

Interaction $p = .01$

Couch et al. (2001) These findings reinforce earlier findings by Couch et al (2001) who reported that the risk associated with smoking increased the most among women with the strongest apparent familial predisposition to breast cancer, as defined as having more familial breast and/or ovarian cancer. Among sisters and daughters in 132 high-risk families, those who ever smoked were at 2.4-fold increased risk of breast cancer (95% CI 1.2-5.1) relative to never-smokers. When the analysis

was restricted to 35 families at highest genetic risk (each containing five breast and/or ovarian cancers), ever-smokers were at 5.8-fold greater risk than nonsmokers (95% CI 1.4-23.9).

10.3 Smoking, Genotypes and Breast Cancer Meta-analyses

Studies of breast cancer, smoking and low-penetrance genetic variants started to appear in the mid 1990s. Different polymorphisms may protect from some carcinogens while enhancing the carcinogenic effect of others. While the myriad combinations of genetic polymorphisms and chemicals is complex, the possible interaction between the NAT2 polymorphism, smoking, and breast cancer has been most intensively investigated. As individual gene-environment interaction studies are almost always underpowered, the focus here is on the three recent meta-analyses and a pooled analysis.

Alberg et al. (2004) reported on a meta-analysis of 9 studies of NAT2, smoking and breast cancer. They found a significantly increased risk among smokers with slow NAT2 acetylation genotypes (meta-RR 1.37; 95% CI 1.19-1.58), but not for smokers with rapid NAT2 acetylation status (meta-RR 1.15; 95% CI 0.97-1.35). The risk for slow NAT2 genotype and smoking was significant only for postmenopausal women (meta-RR 1.6; 95% CI 1.29-2.01; for premenopausal women the meta-RR was 1.10 (95% CI 0.83-1.46).

Terry and Goodman (2006) performed meta-analyses summarizing the findings of the approximately 50 epidemiologic studies that have evaluated a role for genetic polymorphisms related to carcinogen metabolism, modulation of oxidative damage, and DNA repair and the risk of breast cancer related to smoking (see Table 15). Inconsistent results have complicated interpretation. Most of the meta-analyses of specific gene-smoking interaction suffered from a small number of studies, studies with small sample sizes, and varying measures of smoking. However, a fairly consistent positive association was found with long-term smoking among NAT2 slow acetylation genotypes, especially among postmenopausal women. Summary analyses produced overall meta-RR estimates for breast cancer associated with smoking of 1.2 (95% CI 1.0-1.5) for rapid acetylation genotypes and 1.5 (95% CI 1.2-1.8) for slow acetylation genotypes. When analysed by menopausal status, postmenopausal women who smoked and were NAT2 slow acetylation genotypes had a RR of 2.4 (95% CI 1.7-3.3), whereas the other categories were not associated with significant increases in risk. The public health impact is important because 50-60% of Caucasian populations and 35-40% of women of African descent have the NAT2 slow acetylation genotype (Wacholder et al., 2000), as do <25% of Chinese, Japanese, and Koreans and about 70% of Middle Eastern populations (Klaassen, 2001).

Table 15: Summary of Meta-Analyses by Terry and Goodman (2006) of Breast Cancer Smoking and Genotype

Table No.	Genotype ^a	Total No of Cases/Controls	No. of Studies	Odds Ratio (95% CI) ^b	Failsafe Number ^c (# Negative Studies Needed to Nullify Observed OR)
1	NAT2 Rapid	3922/4939	10	1.2 (1.0-1.5)	N/A
	NAT2 Slow	3773/5272	9	1.5 (1.2-1.8)	54
	<i>Premenopausal</i>				
	NAT2 Rapid	1999/2031	5	1.5 (0.9-2.4)	N/A
	NAT2 Slow	1999/2031	5	1.4 (0.9-2.2)	N/A
2	<i>Postmenopausal</i>				
	NAT2 Rapid	2109/2144	6	1.3 (0.8-2.0)	N/A
	NAT2 Slow	2109/2144	6	2.4 (1.7-3.3)	57
3	<i>NAT1*4/*4/*3/*4,3/*3</i>	1469/1646	3 ^d	1.0 (0.7-1.5)	N/A
	<i>NAT1*10</i>	1618/1853	4	1.0 (0.8-1.4)	N/A
4	<i>CYP 1A1 – Wild-type</i>	1370/1470	3	1.3 (1.0-1.6)	N/A
	<i>CYP 1A1 – Any variant</i>	1370/1470	3	1.2 (0.6-2.1)	N/A
5	GSTT1-present	2370/2624	5	1.3 (1.1-1.6)	7
	GSTT1-null	2370/2624	5	1.2 (0.9-1.7)	N/A
	GSTM1-present	2349/2704	6	1.1 (0.8-1.4)	N/A
	GSTM1-null	2349/2704	6	1.4 (1.1-1.9)	11
6	<i>SOD2 Val/Val</i>	2947/3151	4	0.8 (0.2-2.8)	N/A
	<i>SOD2 Ala/Ala</i>	2947/3151	4	1.5 (1.1-2.1)	3
7	<i>XRCC1 194 Arg/Arg</i>	3646/3430	3	1.2 (1.0-1.5)	N/A
	<i>XRCC1 194 Any Trp</i>	3646/3430	3	1.0 (0.7-1.5)	N/A
	<i>XRCC1 399 Arg/Arg</i>	4768/4559	5 ^e	1.1 (0.7-1.7)	N/A
	<i>XRCC1 399 Any Gln</i>	4768/4559	5 ^e	1.1 (0.9-1.4)	N/A

Note: Bolded rows indicate statistically significant increases in summary risk

^a Summary analyses were based on random effects models, which assume that study-specific effect sizes arise from a random distribution of effect sizes with a certain mean and variance

^b Meta-RRs were calculated as weighted averages of the individual study results using inverse variances as the weights

^c In instances where the meta-RR estimates were significantly different from null, we evaluated the potential role of publication bias by calculating the fail-safe number, which expresses the number of missing negative studies, which would be necessary to nullify the observed risk increase (Rosenberg, 2005)

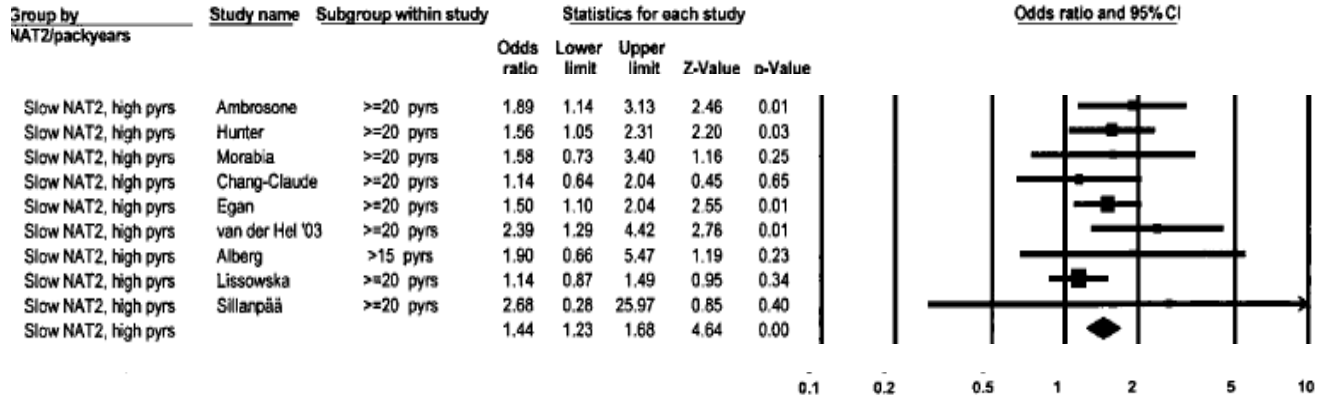
^d Number of studies included for this specific analysis was three, however four stratum-specific ORs were used for the meta-RR analysis, due to one study stratifying Whites and African Americans

^e Number of studies included for this specific analysis was five, however six stratum-specific ORs were used for the meta-RR analysis, due to one study stratifying Whites and African Americans

Ambrosone et al. (2008) reported both a meta-analysis and a pooled analysis using a similar set of studies to Terry and Goodman but with the addition of a large study from Poland (> 2000 cases and 2000 controls) (Lissowska et al., 2006). The meta-analysis included 9 case-control studies and 4 nested case-control studies within cohorts and a total of 4,889 premenopausal and 7,033 postmenopausal women. The meta-analysis found no main effect for *NAT2* status and a statistically significant overall increase in risk for active smoking vs never-active smoking (meta-RR 1.17; 95% CI 1.07-1.27). Among women who smoked, the risk of breast cancer was elevated among those with *NAT2* slow acetylation genotypes (meta-RR 1.27; 95% CI 1.16-1.39), but not for those with rapid *NAT2* genotypes (meta-RR 1.05). Furthermore, pack-years were significantly associated with a dose-dependent increase in risk for slow acetylators, with a relative risk for higher pack-years (≥ 20

pack-years) of 1.44, (95% CI 1.23-1.68) (see Table 16). The individual risk estimates for all nine studies were above 1.0 and four were statistically significant (see Figure 6).

Figure 6: Meta-Analysis of Slow NAT2 Acetylators, Smoking and Breast Cancer Risk for Higher Person-years of Smoking



Source: From Figure 2, Ambrosone et al. (2008)

Ambrosone et al. (2008) also conducted a pooled analysis using raw data requested and received from the authors for 9 (5,201 cases and 5,829 controls) of the original 13 studies. The pooled analysis found results consistent with those from the meta-analysis - with a significant interaction between NAT2 genotypes, smoking and breast cancer risk. An increase in breast cancer risk was observed among NAT2 slow acetylators with greater than 20 pack-years of smoking (one study greater than 15 pack-years) compared to never-active smokers (RR 1.49; 95% CI 1.08-2.04). Increased risks for high pack-years among slow acetylators were similar for premenopausal (OR 1.49; 95% CI 1.08-2.04) and postmenopausal women (OR 1.42; 95% CI 1.16-1.74) (see Table 16).

Table 16: Summary of Meta-Analysis and Pooled Analysis of Smoking Pack-years, NAT2 Acetylators Status, Menopausal Status and Breast Cancer Risk

Type of Analysis	Pack-years ^a	NAT2 Slow Acetylators				NAT2 Rapid Acetylators			
		Premenopausal		Postmenopausal		Premenopausal		Postmenopausal	
		Cases/ Controls	Relative Risk (95% CI)	Cases/ Controls	Relative Risk (95% CI)	Cases/ Controls	Relative Risk (95% CI)	Cases/ Controls	RR (95% CI)
Meta-Analysis	Never active	390/579	1.00	755/879	1.00	278/399	1.00	580/624	1.00
	<20	435/583	1.21 (1.00-1.45)	495/474	1.28 (1.08-1.50)	297/443	1.00 (0.80-1.24)	359/353	1.12 (0.93-1.36)
	≥20	113/107	1.47 (1.08-2.01)	303/257	1.41 (1.15-1.72)	89/86	1.34 (0.94-1.89)	170/206	0.98 (0.77-1.26)
Pooled Analysis	Never active	314/490	1.00	575/701	1.00	222/323	1.00	437/484	1.00
	<20	421/567	1.05 (0.86-1.28)	491/489	1.23 (1.03-1.46)	288/422	0.91 (0.72-1.16)	347/343	1.10 (0.89-1.35)
	≥20	115/110	1.49 (1.08-2.04)	291/249	1.42 (1.16-1.74)	85/87	1.29 (0.89-1.86)	163/201	0.88 (0.69-1.13)

Note: Bolded numbers indicate statistically significant increases in summary risk

^a Pack-years as a categorical variable were available from the following eight studies for meta-analysis: Ambrosone et al., 1996; Morabia et al., 2000; Chang-Claude et al., 2002; Egan et al., 2003; van der Hel et al., 2003; Alberg et al., 2004; Sillanpaa et al., 2005; Lissowska et al., 2006. Pack-years as a categorical variable were available from the following six studies for the pooled analysis: Ambrosone et al., 1996; Morabia et al., 2000; Chang-Claude et al., 2002; Egan et al., 2003; van der Hel et al., 2003; Lissowska et al., 2006.

Source: Ambrosone et al. (2008)

The differences in the *NAT2* genotype and smoking results regarding premenopausal and postmenopausal risk between the two earlier meta-analyses and this most recent one probably reflect slightly different sets of studies included based on slightly different study inclusion criteria, differences in exposure subgroup collapsing, with more detailed analysis of smoking exposure and additional studies in the later meta-analyses (Ambrosone et al., 2008).

10.4 NAT2 Slow Acetylator Genotype and Active Smoking: Application of Causality Criteria

These 3 meta-analyses in combination with the pooled analysis demonstrate a clear pattern of increased breast cancer risk associated with active smoking among women who have the *NAT2* slow acetylator genotypes. The most recent and largest meta-analysis shows a dose-response pattern with higher pack-years of smoking associated with an over 40% increase in risk both for pre- and postmenopausal women. The associated pooled analysis found results consistent with this meta-analysis.

The Panel found these results persuasive when evaluated in light of the criteria for establishing causality:

Consistency:

1. The results are consistent with those of non-genetic studies which have observed identifiable increases in breast cancer risk associated with long-term active smoking in the 10% to 30% range, both in earlier work (Palmer and Rosenberg, 1993), in more recent studies (Terry and Rohan, 2002; California Environmental Protection Agency, 2005), and in reports since 2005 reported in this document.
2. A substantial number of studies contributed to the pooled (9 studies) and meta-analyses (13 studies), representing 4,889 premenopausal and 7,033 postmenopausal women. There was fairly good consistency between studies: all nine risk estimates for more than 20 pack-years of smoking subgroup were between 1.14 and 2.68, and four of the nine estimates statistically significant in the pooled analysis. Although four studies in the meta-analysis found no association, two of these had less than 150 breast cancer cases.
3. The overall consistency in findings between Ambrosone et al.'s 2008 meta-analysis and their pooled analysis, and between the pre- and postmenopausal results add to confidence in the results. Furthermore, their overall results were similar to the earlier meta-analysis by Terry and Goodman (2006).

Strength and Dose-Response

4. There was a strong association between smoking and breast cancer risk among women with the NAT2 slow acetylation genotype - summary risk estimates were 1.44 (95% CI 1.23-1.68) and 1.49 (95% CI 1.08-2.04) for the pooled and meta-analysis respectively, for more than 20 pack-years of smoking. Statistically significant increased summary risk estimates for higher pack-years were observed for both pre- and postmenopausal women, for both the pooled and meta-analyses. Both the low and high pack-years summary risk estimates were statistically significant for the analysis of all women. A dose-response relationship was observed among slow acetylators with risk increased for both low (OR 1.21; 95% CI 1.08-1.35) and even more elevated among high pack-years (OR 1.44; 95% CI 1.23-1.68) compared to never smokers (Ambrosone et al., 2008). Dose-response was also observed for duration of smoking.

Biological Mechanisms

5. There is a biological rationale for a gene-environment interaction between NAT2 slow acetylation status and cigarette smoking, as described by Ambrosone et al (2008), which the Panel found convincing:

“Aromatic amines are a major class of tobacco carcinogens, which include 2-naphthylamine and 4-aminobiphenyl, two compounds known to cause cancer in both animals and humans (Hoffmann et al., 2001; Faraglia et al., 2003). Epidemiologic studies have provided consistent evidence for a causal relationship between aromatic amines and urinary bladder cancer (Naito et al., 1995; Hoffmann and Hoffmann, 1997), and experimental studies have shown that aromatic amines are mammary carcinogens in rodents and humans (Swaminathan et al., 1994; Gorlewska-Roberts et al., 2004). The metabolism of aromatic amines includes the activation and detoxification by metabolic enzymes, such as cytochrome P450s and N-acetyltransferase, and the N-acetylation process by NAT2 is an important detoxification step for aromatic amines (Hein, 2002). Animal models have shown that, upon exposure to aromatic amines, DNA adducts in prostate and bladder tissues were significantly higher in animals with NAT2 slow genotypes (Hein, 2002), and human bladder cancer studies have shown that concentrations of 4-aminobiphenyl-hemoglobin adducts in the blood are significantly higher in slow acetylators than in rapid acetylators, particularly at low levels of carcinogenic exposure (Vineis et al., 1994). In a study of breast tissue, women who smoked and had slow NAT2 genotypes had significantly higher levels of aromatic DNA adducts in breast tissue than women who never smoked and had rapid NAT2 genotypes (Firozi et al., 2002)” (Ambrosone et al., 2008).

Associated Issues

6. **Selection or Recall Bias:** Selection or recall bias is an unlikely explanation for the results. NAT2 status would be unknown to participants and so could not impact on subject response or recall. Four of the studies among the 13 in the meta-analysis and 2 of the 9 in the pooled

analysis were nested in cohort studies and all four suggested increased risk (risk estimates of 1.26 (0.89-1.77), 1.42 (1.09-1.85), 1.47 (0.92-2.37) and 1.87 (0.84-4.14) for *NAT2* slow acetylators who were ever smokers). The nested case-control study is considered to be a robust study design; smoking exposure in three of the four cohorts was ascertained prior to diagnosis, so in those three there is no possibility of diagnosis affecting recall of smoking

7. **Publication Bias:** Ambrosone et al. (2008) report that they did not observe apparent publication bias, influence of missing studies, nor major heterogeneity across studies. The authors reported a slight increase in risk for ever active smoking vs never active smoking with a meta-RR of 1.17; 95% CI 1.07-1.27) with a fail-safe N of 29. The fail-safe number expresses the number of missing negative studies, which would be necessary to nullify the observed risk increase (Rosenberg, 2005).

With 50-60% of Caucasian women, 35-40% of African-American women (Wacholder et al., 2000), about 70% of Middle Eastern women and up to 25% of Chinese, Japanese, and Korean women (Klaassen, 2001), the public health implications of such a risk are important.

10.5 Panel's Judgement on Active Smoking and Breast Cancer Risk

In summary, based on the weight of evidence from: epidemiologic studies, in particular the increased breast cancer risks observed in eight cohort studies for longer duration and/or higher pack-years of smoking; the increased breast cancer risks reported for *NAT2* slow acetylators in pooled and meta-analyses, most notably the recent and in-depth assessment by Ambrosone et al. (2008); studies suggesting higher breast cancer risk with smoking among genetically susceptible familial and *BRCA1* and *BRCA2* subgroups; and its understanding of toxicological and biological mechanisms, the Panel concluded that that the relationship between active smoking and breast cancer is consistent with causality.

11. Secondhand Smoke

SHS has been shown to cause numerous diseases, most notably heart disease and lung cancer (California Environmental Protection Agency, 2005; U.S. Department of Health and Human Services, 2006). More recently, evidence has been accumulating suggesting that SHS contributes to breast cancer (California Environmental Protection Agency, 2005; Johnson, 2005; U.S. Department of Health and Human Services, 2006).

In this section we summarize and compare results and conclusions of two major recent reviews of SHS and breast cancer from the CalEPA (2005) and the U.S. Surgeon General (2006), then summarize studies published since those reports. We conclude with a discussion of the scientific debate over the strengths and limitations of that evidence.

A critical issue in the SHS and breast cancer literature is the quality of the SHS exposure assessment. Although two dozen studies of SHS and breast cancer have been published, only six have collected a lifetime history of SHS exposure. When exposure assessment is inadequate, some exposed cases and controls will be classified as unexposed, thus contaminating the referent group. Where a small percentage of a population has exposure (typically in occupational epidemiology below 10% of the population), this type of exposure misclassification is likely to have a small dilution effect on any underlying risk. However, when an exposure like SHS is considered, the vast majority of population may be exposed (lifetime assessments typically find 80 to 95% of Western female populations with regular residential and/or occupational SHS exposure). In this case, inadequate SHS exposure assessment (for example, ignoring occupational exposure) can result in the majority of those categorized as “unexposed” actually having been exposed to SHS, thus seriously contaminating the referent group and leading to underestimates of risks, if they should exist.

11.1 Secondhand Smoke and Breast Cancer Literature

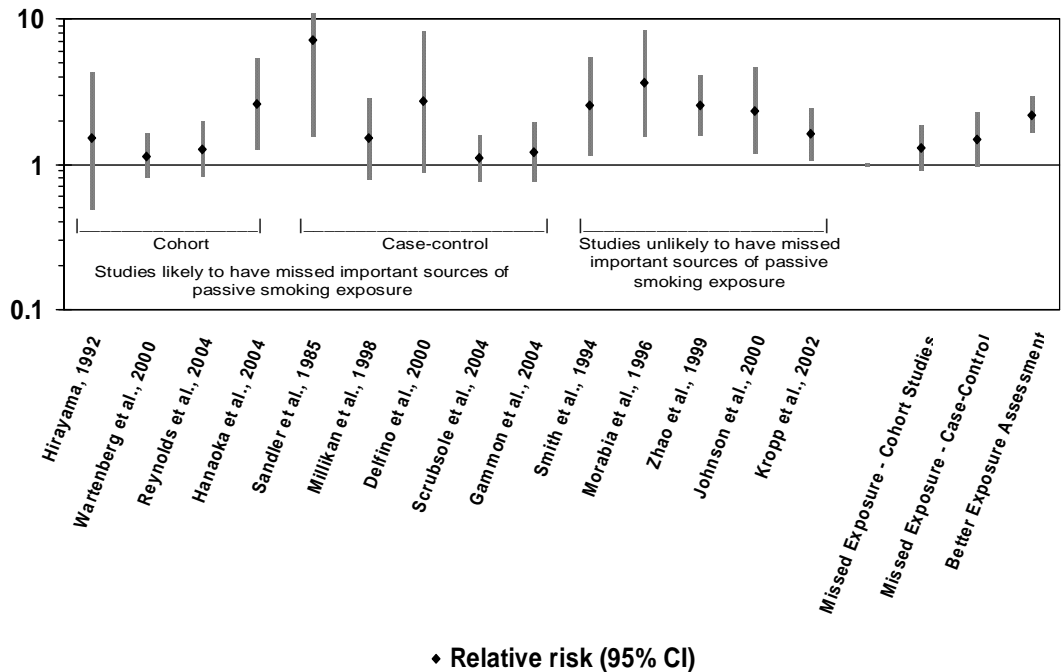
International Agency for Research on Cancer (IARC) Report

A working group of the International Agency for Research on Cancer (2004) concluded that there was no association between either active or passive smoking and breast cancer. For active smoking they relied on the Collaborative Group meta-analysis of 53 studies (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). For SHS they noted the lack of increased risk reported in two large U. S. cohort studies (Wartenberg et al., 2000; Egan et al., 2002), and that the lack of an active smoking risk made a risk from SHS unlikely. They provided neither summary estimates of SHS risk, nor estimates for active smoking risk after controlling for SHS.

California Environmental Protection Agency Report

The CalEPA issued a report on the health effects of environmental tobacco smoke (California Environmental Protection Agency, 2005). They calculated a relative risk of 1.68 (95% CI 1.33-2.12) for breast cancer among younger, primarily premenopausal women who had never smoked, associated with regular exposure to SHS, based on 14 studies. Figure 7 summarizes that evidence, separating out the studies by study type – case-control or cohort – and by the completeness of the SHS exposure assessment. For older women, the CalEPA found some evidence that environmental tobacco smoke was associated with breast cancer, but that the evidence was inconclusive. The CalEPA meta-analysis expanded on the meta-analysis by Johnson (2005). With regard to breast cancer they concluded that “the evidence for exposure to environmental tobacco smoke and breast cancer is consistent with causality in younger, primarily premenopausal women.”

Figure 7: Meta-analysis of Secondhand Smoke and Breast Cancer Risk in Younger, Primarily Premenopausal Women Who Never Smoked



Note: For Reynolds et al., 2004, new risk estimate from Reynolds et al. letter (2006) presented for women exposed in childhood and adulthood (risk for all exposed women not reported).

U.S. Surgeon General's Report, 2006

The U.S. Surgeon General's Report also covered health effects of exposure to SHS (U.S. Department of Health and Human Services, 2006). With regard to breast cancer, the report considered, by and large, the same SHS evidence as the CalEPA report. The Surgeon General reported a pooled estimate of risk of 1.64 (95% CI 1.25-2.14) for the 11 studies reporting on premenopausal breast cancer and SHS (see Table 17). For postmenopausal women, they observed no increase in risk with the metrics of SHS and breast cancer they examined (U.S. Department of Health and Human Services, 2006). The Surgeon General's report, like the IARC report stated that there was no association between active smoking and breast cancer, and like the IARC report referenced in particular the Oxford Collaborative Group on Hormonal Factors in Breast Cancer (2002) meta-analysis. They concluded "The evidence is suggestive but not sufficient to infer a causal relationship between second-hand smoke and breast cancer" (U.S. Department of Health and Human Services, 2006).

Table 17: Summary Risk Estimates for Breast Cancer Risk Associated with Ever Regular Secondhand Smoke Exposure in the California EPA and U.S. Surgeon General's Reports

Exposure	California EPA Report (2005)		U.S. Surgeon General's Report (2006)	
	N	Relative Risk (95% CI)	N	Relative Risk (95% CI)
All studies	19	1.25 (1.08-1.44)	21	1.20 (1.08-1.35)
Premenopausal or Women < 50 (California EPA)	14	1.68 (1.31-2.15)	11	1.64 (1.25-2.14)
Premenopausal (Surgeon General)				
Premenopausal – Studies with lifetime exposure assessment	5	2.20 (1.69-2.87)	6	1.85 (1.19-2.87)
Postmenopausal	9	^a	10	1.00 (0.88-1.12)

^a The CalEPA reported no summary risk estimate but concluded the 9 postmenopausal risk estimates for ever regular exposure “cluster around a null association”

California EPA Summary

Miller et al. (2007) published a summary of the CalEPA report breast cancer findings and presented an extended discussion of potential biases and other concerns expressed during the CalEPA's formal public consultation period for the large report. The concerns included: strength of association, potential for confounding, publication bias, case-control vs cohort studies and the tension between potential for recall bias in case-control studies and exposure misclassification and risk dilution in cohort studies with poor exposure assessment, controversies regarding the relative potency of active vs SHS, the discord between premenopausal and postmenopausal risk, the potential role of anti-estrogenicity of active smoking and windows of susceptibility. The paper concluded that these further assessments of the evidence did not change the CalEPA conclusion and the authors reiterated the conclusion that SHS risk for younger primarily premenopausal women and breast cancer was consistent with causality.

11.2 More Recent Studies of SHS and Premenopausal Breast Cancer

Since the CalEPA report was completed, four studies of SHS and breast cancer that present results in younger women have been published. They continued to show the same patterns of breast cancer risk related to SHS exposure as the CalEPA and U.S. Surgeon General's meta-analyses demonstrated. The one study that collected lifetime SHS exposure data and analysed the SHS risk in comparison to the group reporting no SHS exposure (Lissowska et al., 2006) reported increased risk among premenopausal women for SHS exposure and for active smoking, while those with poorer exposure assessment or analysis did not observe increased risk. The studies and results are briefly described here:

Bonner et al. (2005) A large case-control study in the USA (Bonner et al., 2005) collected lifetime SHS information. However, no analyses used a reference group consisting of women who were unexposed both at home and at work. Instead, the referent for home exposure contained subjects

who had been exposed at work, and the occupational referent contained subjects who had been exposed at home. Results were included in the Surgeon General's report and were mixed, with residential exposures suggesting inconsistent increases in breast cancer risk and occupational exposure suggesting reduced risk.

Lissowska et al. (2007) A large Polish case-control study involving collaboration with the U.S. National Cancer Institute was published recently (Lissowska et al., 2006). Active smoking risks were not presented by menopausal status, but women under 45 had an active smoking risk of 1.95 (95% CI 1.38-2.76). In a re-analysis published by Lissowska et al. as a response to a letter to the editor (Johnson, 2007), increasing premenopausal breast cancer risks were observed for increasing levels of total SHS exposure: 1.36 (95% CI 0.67-1.39); 1.52 (0.73-3.13) and 2.02 (0.94-4.36), for exposures of <100, 101–200, and >200 (h/day-years) respectively (test for trend p-value, 0.08) (Lissowska et al., 2007).

Roddam et al. (2007) In a large study of breast cancer in women aged 36-45 in Britain, Roddam et al. (2007) did not find increased risk for SHS (RR 0.89; 95% CI 0.64-1.25) but they evaluated only spousal SHS exposure, reported by only 41% of the never-smoker cases. Another study of SHS and breast cancer in young women in Britain, (Smith et al., 1994) also based on young breast cancer cases diagnosed in the late 1980s, found 93% of the premenopausal never-smoker cases had had SHS exposure –based on a lifetime exposure assessment (childhood, adult residential and occupational), similar to the other SHS-breast cancer studies with detailed exposure measures. A priori, one would not have expected much increase in risk in the Roddam study because of extensive degree of exposure misclassification.

Pirie et al. (2008) A recent analysis of the British Million Women Study cohort identified 2,518 breast cancers among a cohort of women age 53 to 67 who were followed an average of 3.5 years (Pirie et al, 2008). Childhood SHS was ascertained by asking about parental smoking at age 0 and age 10. Adult exposure was limited to current exposure to SHS from a spouse (at about age 53 to 67). Only 11% of the women never smokers were categorized as exposed to SHS as adults. Increased breast cancer risk with SHS exposure was not observed for childhood or adult exposure.

In the same article Pirie et al. (2008) also presented a meta-analysis of the SHS-breast cancer literature, but they did not perform subgroup analysis by menopausal status, age or quality of the SHS exposure measures, as the CalEPA and U.S. Surgeon General had done. They found no overall increase in risk for the prospective studies and a small overall increase in risk for the retrospective studies, results consistent with the overall breast cancer risks reported by the CalEPA (California Environmental Protection Agency, 2005) and the U.S. Surgeon General (U.S. Department of Health and Human Services, 2006). Pirie et al. (2008) argued against a SHS-breast cancer risk and suggested that because the prospective studies did not find an effect, the risk observed among retrospective studies was likely explained by recall bias.

Unlike Pirie et al. (2008), the Expert Panel felt that subgroup analysis was not only valid, but also necessary, given the wide variation in the quality of the SHS exposure measures and potential for non-differential exposure misclassification of SHS to obscure risks. Several of the prospective studies had very incomplete measures of exposure to SHS, like the British Million Women Study. None of the prospective studies included lifetime assessments of SHS in residential and occupational settings, whereas the 5 retrospective studies that observed higher increases in premenopausal breast cancer risk did so. The Panel did not feel that the prospective studies could be relied on given the potential for serious contamination of the SHS “unexposed” referent groups with inadequate SHS measures. Furthermore, the Panel noted that 3 of the 4 Asian cohort studies (where SHS exposures may have tended to be limited for women to residential exposures), did suggest SHS dose-response relationships, but that the meta-analyses looked at risks associated with ever regular exposure only.

11.3 Causal or Suggestive? The Debate Over the Evidence

Given that the CalEPA and U.S. Surgeon General calculated similar elevated summary risk estimates for breast cancer among younger women associated with SHS exposure, the question may arise why they reached different conclusions on causality.

The U.S. Surgeon General’s Report states at the beginning of its breast cancer section that because a very large meta-analysis of active smoking and breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002) did not find an increased risk, it is difficult to accept a SHS risk (U.S. Department of Health and Human Services, 2006). As indicated in the active smoking section, this pooled analysis included only smoking status (ever/never, current/former), and did not address risk with regard to the intensity of smoking, duration of smoking or timing of smoking (e.g., before first pregnancy). This analysis also did not control for SHS and premenopausal breast cancer was not targeted for thorough analysis. Furthermore, the U.S. Surgeon General’s Report did not examine in detail the active smoking literature after 2002.

In contrast, the CalEPA’s assessment included evaluation of studies through 2005 on active smoking and breast cancer including several more recent studies of active smoking that carefully controlled for SHS exposure. For women who had smoked, the breast cancer risk estimate was 1.46 (95% CI 1.15-1.85) compared to nonsmoking women not exposed to SHS (Johnson, 2005). Furthermore, the CalEPA reported on six recent prospective cohort studies that each found statistically-significant increased breast cancer risks associated with at least some measure of active smoking (California Environmental Protection Agency, 2005).

Case-control vs Cohort Studies of SHS and Breast Cancer and the Potential Impact of SHS Exposure Misclassification on Observed Risks

In general, the Panel considered evidence from cohort studies to be superior to that from case-control studies because the potential for bias in reporting of exposures by disease status is eliminated in cohort studies. However, challenges in collecting detailed exposure information in cohort studies may result in a greater potential for misclassification of exposure than for case-control studies which were designed to collect detailed exposure histories. Three large North American cohort studies have not observed increases in breast cancer risk with SHS exposure. However, these cohort studies (similar to the case-control studies with poorer exposure assessments) could not adequately identify all women who had been regularly exposed to SHS. For example, in the main analysis of the Cancer Prevention Study-II American cohort study (Wartenberg et al., 2000), SHS exposure information included a history of spousal smoking, but assessment of workplace and other household exposure was limited to exposure in a single year – 1982. The study did not collect information on the history of workplace, childhood or non-husband residential SHS exposure for the women.

In a North American study, failing to measure these SHS exposures is likely to result in important misclassification of exposure status (Johnson, 2001). In the dose-response analysis, only 50% of women were categorized as exposed to SHS (Wartenberg et al., 2000). However, other studies that examined major sources of SHS exposure, including residential, workplace and sometimes social exposure, have found 80% to 95% of the women who were never-smokers reported having had regular exposure to SHS during some periods of their lives (Fontham et al., 1994; Johnson et al., 2000). In the Nurses' Health Study, another large North American cohort study (Egan et al., 2002), the exposure assessment was likely inadequate (Johnson and Wells, 2002). For example, they collected only current exposure in 1982 in their evaluation of nurses' workplace SHS exposure (Johnson, 2002). The third study on California teachers has reported only on residential exposure to date (Reynolds et al., 2004).

Inadequate SHS Exposure Assessment and Active Smoking Risks

Exposure misclassification will dilute estimations of risk for active smoking as well as for SHS. Since most studies of active smoking and breast cancer have not adequately accounted for lifetime exposure to SHS it is fair to conclude that most studies underestimate the risk of active smoking for breast cancer because they are unable to account for the exposure to SHS in the cases and non-cases. In Section 10, it was observed that most studies of active smoking and breast cancer reported some increase in risk for the most highly exposed groups, whether measured by duration of smoking or smoking intensity. This observation, together with the likely effect of dilution of observed risk due to misclassification supports the conclusion that a real increase in risk of breast cancer has been consistently underestimated in many studies.

Exposure Response Relationship Between Smoking and Breast Cancer and the Potential Impact of SHS Exposure Misclassification on Observed Risks

Perhaps the most important factor that made it difficult for previous expert groups to conclude that there was a causal relationship between SHS and breast cancer had been the failure to observe an association with active smoking. However, cohort studies with duration and pack-year assessment of smoking have generally noted increases in breast cancer risk of the order of 10-30%. As well, because of the misclassification of SHS exposure, which is likely to bias risk estimates downward among younger women in particular, the true increase in risk is likely to be greater than 10-30%.

As noted above, a meta-analysis of 19 studies of breast cancer and SHS exposure (Johnson, 2005) that also evaluated active smoking risk among studies that had controlled for SHS exposure (therefore comparing smokers to women with neither active nor SHS) found a breast cancer risk estimate for women who had smoked of 1.46 (95% CI 1.15-1.85) based on 13 studies. For the 5 studies considered to have the best assessment of SHS, the active smoking risk was more than double (RR 2.08 (95% CI 1.44-3.01)), whereas the active smoking risk estimate for the 8 other studies was 1.15 (95% CI 0.92-1.43).

Explaining the Similarity of Active and Passive Smoking (SHS) Risks

An unresolved issue is why the risks associated with SHS appear to be similar to those associated with active smoking when SHS is properly controlled. This is not the case for lung cancer or other smoking-related cancers. One explanation which has been offered is based on the relative difference in anti-estrogenic effects there may be between active and passive smoking (Morabia et al, 2001). However, more research into this issue is clearly necessary. It is notable that Vineis et al. (1994) found that women exposed to SHS had more DNA adducts than active smokers.

Passive smoking risk could also be magnified by a “low dose effect” similar to that proposed for colon cancer (Vineis and McMichael, 1996) where the modifying effect of a genotype might be more apparent at low doses. Furthermore, women who smoke are at higher risk than nonsmokers for conditions related to estrogen deficiency such as osteoporotic fracture, earlier menopause and at lower risk of endometrial cancer, fibrocystic disease and vomiting during pregnancy; conditions which are related to excess estrogen (Baron et al., 1990). With total estrogen a surrogate for breast cancer risk, the antiestrogenic effects associated with active smoking might depress the level of breast cancer risk related to tobacco smoke in active smokers but not be strong enough in women passively exposed to depress their tobacco-related risk (Johnson, 2005).

Another possible explanation is that there is a low threshold effect where the pathways become saturated at a relatively low level of exposure to tobacco smoke (in the SHS dose range) and further exposure does not result in further risk.

11.4 Panel's Judgement on Secondhand Smoke Exposure and Breast Cancer Risk

In summary, based on the weight of evidence presented in the CalEPA and the U.S. Surgeon General reports, a similar pattern of risks in individual SHS-breast cancer studies published since these reports, its understanding of toxicological and biological mechanisms, and strong recent evidence of increased breast cancer risk associated with active smoking, the Panel concurred with the CalEPA's earlier assessment that the relationship between SHS and breast cancer in younger, primarily premenopausal women is consistent with causality. The evidence on SHS and postmenopausal breast cancer was considered insufficient to make a determination of causality.

12. Other Considerations

The Panel noted that comprehensive health communication strategies have repeatedly been found to be vital parts of comprehensive tobacco control. In Canada, there has been some ebb and flow in the components of tobacco control strategies, but communication strategies have been a constant and continuous part of tobacco control since the inception of government-led tobacco control in 1964. They have been successfully used to inform health professionals and the general public of health risks of exposure to tobacco smoke continuously for 45 years, and will continue for years to come. (Department of National Health and Welfare, 1966). A call for more education, communication, and increasing of public awareness about the dangers of tobacco are key features of the Framework Convention on Tobacco Control, an international treaty with 162 Parties, including Canada (World Health Organization, 2005).

Well-designed comprehensive health communications strategies could be effective at communicating the risk of breast cancer from exposure of women, particularly girls and young women, to tobacco smoke, whether through active smoking or exposure to SHS. There is a growing body of literature demonstrating the effectiveness of prominent health warnings on cigarette packages conveying information about the many risks of tobacco smoke. The work of the International Tobacco Control Policy Evaluation Project is particularly informative in this regard (Hammond et al., 2006). Recent consumer research commissioned by Health Canada revealed that the most effective health warnings would be those that occupied 100% of each of the front and back of cigarette packages (Les Etudes de Marche Createc, 2008).

13. Conclusions

Causality

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

Secondhand Smoke: Based primarily on the evidence presented by the CalEPA and the Surgeon General, and strong recent evidence of an active smoking-breast cancer risk, the Panel concluded that the relationship between SHS and breast cancer in younger, primarily premenopausal women is consistent with causality. The evidence was considered insufficient to pass judgement on SHS and postmenopausal breast cancer.

Estimating Incidence and Mortality

The Panel concluded that it would be premature at this time to estimate breast cancer incidence and mortality attributable to active and passive smoking, but that this could be a topic for further research.

Research Recommendations

The Panel recommends that research be undertaken to further consolidate and synthesize knowledge of the relationship between breast cancer and tobacco smoke. Such research would be facilitated by establishing uniform standards and protocols for research on breast cancer and tobacco smoke to ensure greater comparability of future research projects. Possible projects could include:

- Additional case-control and prospective studies of the relationship of active and passive smoking to pre- and postmenopausal breast cancer with comprehensive measures of lifetime exposure to tobacco smoke.
- Estimations of population attributable risk of breast cancer incidence and mortality attributable to smoking.
- Quantitative meta-analyses of active smoking and breast cancer focusing on risk related to age at smoking initiation, smoking before pregnancy, and the high duration/ high pack-years smoking.
- Further research on breast cancer and tobacco smoke in subgroups of women stratified by *NAT2* genotype. Further confirmation of the most recent findings would be beneficial.

The Panel also proposes investigator conferences to seek the maximum pooling possible of research finding on breast cancer and tobacco smoke .

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.

14. References

- Adami, H.O., Lund, E., Bergstrom, R., Meirik, O. 1988. Cigarette smoking, alcohol consumption and risk of breast cancer in young women. *Br. J Cancer* 58, 832-837.
- Al-Delaimy, W.K., Cho, E., Chen, W.Y., Colditz, G., Willet, W.C. 2004. A prospective study of smoking and risk of breast cancer in young adult women. *Cancer Epidemiol. Biomarkers Prev.* 13, 398-404.
- Albanes, D., Jones, D.Y., Micozzi, M.S., Mattson, M.E. 1987. Associations between smoking and body weight in the US population: analysis of NHANES II. *Am. J Public Health* 77, 439-444.
- Alberg, A.J., Daudt, A., Huang, H.Y., Hoffman, S.C., Comstock, G.W., Helzlsouer, K.J., Strickland, P.T., Bell, D.A. 2004. N-acetyltransferase 2 (NAT2) genotypes, cigarette smoking, and the risk of breast cancer. *Cancer Detect. Prev.* 28, 187-193.
- Ambrosone, C.B., Freudenheim, J.L., Graham, S., Marshall, J.R., Vena, J.E., Brasure, J.R., Michalek, A.M., Laughlin, R., Nemoto, T., Gillenwater, K.A., Shields, P.G. 1996. Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *JAMA* 276, 1494-1501.
- Ambrosone, C.B., Kropp, S., Yang, J., Yao, S., Shields, P.G., Chang-Claude, J. 2008. Cigarette smoking, N-acetyltransferase 2 genotypes, and breast cancer risk: pooled analysis and meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 17, 15-26.
- Ambrosone, C.B., Shields, P.G., 1997. Molecular epidemiology of breast cancer. *Prog. Clin. Biol. Res.* 396, 83-99.
- Band, P.R., Le, N.D., Fang, R., Deschamps, M., 2002. Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet* 360, 1044-1049.
- Baron, J.A. 1984. Smoking and estrogen-related disease. *Am. J Epidemiol.* 119, 9-22.
- Baron, J.A., La Vecchia, C., Levi, F. 1990. The antiestrogenic effect of cigarette smoking in women. *Am. J Obstet Gynecol.* 162, 502-514.
- Baron, J.A., Newcomb, P.A., Longnecker, M.P., Mittendorf, R., Storer, B.E., Clapp, R.W., Bogdan, G., Yuen, J. 1996. Cigarette smoking and breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 5, 399-403.
- Bennicke, K., Conrad, C., Sabroe, S., Sorensen, H.T. 1995. Cigarette smoking and breast cancer. *BMJ* 310, 1431-1433.
- Bonner, M.R., Nie, J., Han, D., Vena, J.E., Rogerson, P., Muti, P., Trevisan, M., Edge, S.B., Freudenheim, J.L. 2005. Secondhand smoke exposure in early life and the risk of breast cancer among never smokers (United States). *Cancer Causes Control* 16, 683-689.
- Braga, C., Negri, E., La Vecchia, C., Filiberti, R., Franceschi, S. 1996. Cigarette smoking and the risk of breast cancer. *Eur. J Cancer Prev.* 5, 159-164.
- Breast Cancer Family Registry, Kathleen Cuninghame Consortium for Research into Familial Breast Cancer (Australasia), Ontario Cancer Genetics Network (Canada). 2008. Smoking and risk of breast cancer in carriers of mutations in BRCA1 or BRCA2 aged less than 50 years. *Breast Cancer Res. Treat.* 109, 67-75.
- Brinton, L.A., Schairer, C., Stanford, J.L., Hoover, R.N. 1986. Cigarette smoking and breast cancer. *Am. J Epidemiol.* 123, 614-622.
- Brownson, R.C., Blackwell, C.W., Pearson, D.K., Reynolds, R.D., Richens, J.W., Jr., Papermaster, B.W. 1988. Risk of breast cancer in relation to cigarette smoking. *Arch. Intern. Med.* 148, 140-144.
- Brunet, J.S., Ghadirian, P., Rebbeck, T.R., Lerman, C., Garber, J.E., Tonin, P.N., Abrahamson, J., Foulkes, W.D., Daly, M., Wagner-Costalas, J., Godwin, A., Olopade, O.I., Moslehi, R., Liede, A., Futreal, P.A., Weber, B.L., Lenoir, G.M., Lynch, H.T., Narod, S.A. 1998. Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. *J Natl. Cancer Inst.* 90, 761-766.
- California Environmental Protection Agency. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant <http://www.arb.ca.gov/regact/ets2006/ets2006.htm> (accessed 25-03-2009). 2005.

Calle, E.E., Miracle-McMahill, H.L., Thun, M.J., Heath, C.W., Jr. 1994. Cigarette smoking and risk of fatal breast cancer. *Am. J. Epidemiol.* 139, 1001-1007.

Canadian Cancer Society, la Coalition québécoise pour le contrôle du tabac, HealthBridge, the Non-Smokers' Rights Association, the Ontario Tobacco Research Unit, Physicians for a Smoke-Free Canada. *The Framework Convention on Tobacco Control in Canada. A Civil Society 'Shadow Report'*. 2009.

Cavalieri, E.L., Higginbotham, S., RamaKrishna, N.V., Devanesan, P.D., Todorovic, R., Rogan, E.G., Salmasi, S. 1991. Comparative dose-response tumorigenicity studies of dibenzo[alpha,]pyrene versus 7,12-dimethylbenz[alpha]anthracene, benzo[alpha]pyrene and two dibenzo[alpha,]pyrene dihydrodiols in mouse skin and rat mammary gland. *Carcinogenesis* 12, 1939-1944.

Cavalieri, E.L., Rogan, E.G., Higginbotham, S., Cremonesi, P., Salmasi, S. 1989. Tumor-initiating activity in mouse skin and carcinogenicity in rat mammary gland of dibenzo[a]pyrenes: the very potent environmental carcinogen dibenzo[a, l]pyrene. *J Cancer Res. Clin. Oncol.* 115, 67-72.

Centers for Disease Control and Prevention. *Smoking and Tobacco: Percentage of young adults who were current, former or never smokers overall and by sex, race, and education.* 2007.

Centers for Disease Control and Prevention. *Health Effects of Cigarette Smoking.* Fact Sheet. 2008.

Centers for Disease Control and Prevention. 2002. Annual smoking-attributable mortality, years of potential life lost, and economic costs--United States, 1995-1999. *MMWR Morb. Mortal. Wkly. Rep.* 51, 300-303.

Chang-Claude, J., Kropp, S., Jager, B., Bartsch, H., Risch, A. 2002. Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 11, 698-704.

Chen, C., Wang, X., Wang, L., Yang, F., Tang, G., Xing, H., Ryan, L., Lasley, B., Overstreet, J.W., Stanford, J.B., Xu, X. 2005. Effect of environmental tobacco smoke on levels of urinary hormone markers. *Environ. Health Perspect.* 113, 412-417.

Chu, S.Y., Stroup, N.E., Wingo, P.A., Lee, N.C., Peterson, H.B., Gwinn, M.L. 1990. Cigarette smoking and the risk of breast cancer. *Am. J. Epidemiol.* 131, 244-253.

Colditz G.A., Baer H.J., Tamimi R.M. 2006. Breast Cancer. In: Schottenfeld D., Fraumeni J.F. Jr. (Eds), *Cancer Epidemiology and Prevention.* Oxford University Press, New York, pp. 995-1012.

Colilla, S., Kantoff, P.W., Neuhausen, S.L., Godwin, A.K., Daly, M.B., Narod, S.A., Garber, J.E., Lynch, H.T., Brown, M., Weber, B.L., Rebbeck, T.R. 2006. The joint effect of smoking and AIB1 on breast cancer risk in BRCA1 mutation carriers. *Carcinogenesis* 27, 599-605.

Collaborative Group on Hormonal Factors in Breast Cancer. 2002. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br. J. Cancer* 87, 1234-1245.

Cui, Y., Miller, A.B., Rohan, T.E. 2006. Cigarette smoking and breast cancer risk: update of a prospective cohort study. *Breast Cancer Res. Treat.* 100, 293-299.

Delfino, R.J., Smith, C., West, J.G., Lin, H.J., White, E., Liao, S.Y., Gim, J.S., Ma, H.L., Butler, J., Anton-Culver, H. 2000. Breast cancer, passive and active cigarette smoking and N-acetyltransferase 2 genotype. *Pharmacogenetics* 10, 461-469.

Department of National Health and Welfare. *The Canadian Smoking and Health Program.* 1966. Ottawa, Canada.

Egan, K.M., Stampfer, M.J., Hunter, D., Hankinson, S., Rosner, B.A., Holmes, M., Willett, W.C., Colditz, G.A. 2002. Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. *Epidemiology* 13, 138-145.

Ewertz, M. 1990. Smoking and breast cancer risk in Denmark. *Cancer Causes Control* 1, 31-37.

Faraglia, B., Chen, S.Y., Gammon, M.D., Zhang, Y., Teitelbaum, S.L., Neugut, A.I., Ahsan, H., Garbowski, G.C., Hibshoosh, H., Lin, D., Kadlubar, F.F., Santella, R.M. 2003. Evaluation of 4-aminobiphenyl-DNA adducts in human breast cancer: the influence of tobacco smoke. *Carcinogenesis* 24, 719-725.

- Field, N.A., Baptiste, M.S., Nasca, P.C., Metzger, B.B. 1992. Cigarette smoking and breast cancer. *Int. J Epidemiol.* 21, 842-848.
- Fink, A.K., Lash, T.L. 2003. A null association between smoking during pregnancy and breast cancer using Massachusetts registry data (United States). *Cancer Causes Control* 14, 497-503.
- Firozi, P.F., Bondy, M.L., Sahin, A.A., Chang, P., Lukmanji, F., Singletary, E.S., Hassan, M.M., Li, D. 2002. Aromatic DNA adducts and polymorphisms of CYP1A1, NAT2, and GSTM1 in breast cancer. *Carcinogenesis* 23, 301-306.
- Fontham, E.T., Correa, P., Reynolds, P., Wu-Williams, A., Buffler, P.A., Greenberg, R.S., Chen, V.W., Alterman, T., Boyd, P., Austin, D.F. 1994. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *JAMA* 271, 1752-1759.
- Gammon, M.D., Eng, S.M., Teitelbaum, S.L., Britton, J.A., Kabat, G.C., Hatch, M., Paykin, A.B., Neugut, A.I., Santella, R.M. 2004. Environmental tobacco smoke and breast cancer incidence. *Environ. Res.* 96, 176-185.
- Gammon, M.D., Schoenberg, J.B., Teitelbaum, S.L., Brinton, L.A., Potischman, N., Swanson, C.A., Brogan, D.J., Coates, R.J., Malone, K.E., Stanford, J.L. 1998. Cigarette smoking and breast cancer risk among young women (United States). *Cancer Causes Control* 9, 583-590.
- Ghadirian, P., Lubinski, J., Lynch, H., Neuhausen, S.L., Weber, B., Isaacs, C., Baruch, R.G., Randall, S., Ainsworth, P., Friedman, E., Horsman, D., Tonin, P., Foulkes, W.D., Tung, N., Sun, P., Narod, S.A. 2004. Smoking and the risk of breast cancer among carriers of BRCA mutations. *Int. J Cancer* 110, 413-416.
- Ginsburg, O., Ghadirian, P., Lubinski, J., Cybulski, C., Lynch, H., Neuhausen, S., Kim-Sing, C., Robson, M., Domchek, S., Isaacs, C., Klijn, J., Armel, S., Foulkes, W.D., Tung, N., Moller, P., Sun, P., Narod, S.A. 2009. Smoking and the risk of breast cancer in BRCA1 and BRCA2 carriers: an update. *Breast Cancer Res. Treat.* 114, 127-135.
- Goodman, M.T., Cologne, J.B., Moriwaki, H., Vaeth, M., Mabuchi, K. 1997. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors. *Prev. Med.* 26, 144-153.
- Gorlewska-Roberts, K.M., Teitel, C.H., Lay, J.O., Jr., Roberts, D.W., Kadlubar, F.F. 2004. Lactoperoxidase-catalyzed activation of carcinogenic aromatic and heterocyclic amines. *Chem. Res. Toxicol.* 17, 1659-1666.
- Gram, I.T., Braaten, T., Terry, P.D., Sasco, A.J., Adami, H.O., Lund, E., Weiderpass, E. 2005. Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol. Biomarkers Prev.* 14, 61-66.
- Gronwald, J., Byrski, T., Huzarski, T., Cybulski, C., Sun, P., Tulman, A., Narod, S.A., Lubinski, J. 2006. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. *Breast Cancer Res. Treat.* 95, 105-109.
- Ha, M., Mabuchi, K., Sigurdson, A.J., Freedman, D.M., Linet, M.S., Doody, M.M., Hauptmann, M. 2007. Smoking cigarettes before first childbirth and risk of breast cancer. *Am. J. Epidemiol.* 166, 55-61.
- Hammond, D., Fong, G.T., McNeill, A., Borland, R., Cummings, K.M. 2006. Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control (ITC) Four Country Survey. *Tob. Control* 15 Suppl 3, iii19-iii25.
- Hecht, S.S. 2002. Tobacco smoke carcinogens and breast cancer. *Environ. Mol. Mutagen.* 39, 119-126.
- Hein, D.W. 2002. Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. *Mutat. Res.* 506-507, 65-77.
- Hoffman, M., Hecht SS, 1989. Advances in tobacco carcinogenesis. In: Grover P (Ed.), *Handbook of Experimental Pharmacology*, 1988. Springer-Verlag.
- Hoffmann, D., Hoffmann, I. 1997. The changing cigarette, 1950-1995. *J. Toxicol. Environ. Health* 50, 307-364.
- Hoffmann, D., Hoffmann, I., El-Bayoumy, K. 2001. The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. *Chem. Res. Toxicol.* 14, 767-790.

Hunter, D.J., Hankinson, S.E., Hough, H., Gertig, D.M., Garcia-Closas, M., Spiegelman, D., Manson, J.E., Colditz, G.A., Willett, W.C., Speizer, F.E., Kelsey, K. 1997. A prospective study of NAT2 acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis* 18, 2127-2132.

Husten, C.G., Chrismon, J.H., Reddy, M.N. 1996. Trends and effects of cigarette smoking among girls and women in the United States, 1965-1993. *J Am Med. Womens Assoc.* 51, 11-18.

International Agency for Research on Cancer, 2000. *Cancer Incidence in Five Continents*. Lyon, France, IARC Press.

IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83. *Tobacco Smoke and Involuntary Smoking*. 2004. Lyon, France, IARC Press.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, *Tobacco Smoke and Involuntary Smoking*. 2004.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 38, *Tobacco Smoking*. 1986. Lyon, France, IARC Press.

International Agency for Research on Cancer. IARC Handbooks on Cancer Prevention, Vol 6, *Weight Control and Physical Activity*. 2002. Lyon, France, IARC Press,

International Agency for Research on Cancer. IARC Monograph on Printing Processes and Printing Inks, Carbon Black and Some Nitrocompounds. 1996 Lyon, France, WHO.

International Agency for Research on Cancer. IARC Monograph on Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds. 1973. Lyon, France, WHO.

International Agency for Research on Cancer. IARC Monographs on Some Industrial Chemicals. 1994. Lyon, France, WHO.

Innes, K.E., Byers, T.E. 2001. Smoking during pregnancy and breast cancer risk in very young women (United States). *Cancer Causes Control* 12, 179-185.

Johnson, K.C. 2001. Re: Passive smoking exposure and female breast cancer mortality. *J Natl Cancer Inst* 93, 719-720.

Johnson, K.C. 2005. Accumulating evidence on passive and active smoking and breast cancer risk. *Int. J. Cancer* 117, 619-628.

Johnson, K.C. 2007. Re: more data regarding the effects of passive smoking on breast cancer risk among younger women. *Int. J. Cancer* 120, 2519-2520.

Johnson, K.C., Hu, J., Mao, Y., The Canadian Cancer Registries Epidemiology Research Group, 2000. Passive and active smoking and breast cancer risk in Canada, 1994-97. *Cancer Causes Control* 11, 211-221.

Johnson, K.C., Wells, A.J., 2002. Active and passive smoking in breast cancer. *Epidemiology* 13, 745-746.

Kelsey, J.L. 1993. Breast cancer epidemiology: summary and future directions. *Epidemiol. Rev.* 15, 256-263.

Klaassen, C. 2001. *Casarett & Doull's Toxicology: The Basic Science of Poisons*. McGraw-Hill, New York.

Kropp, S., Chang-Claude, J. 2002. Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am. J. Epidemiol.* 156, 616-626.

Lash, T.L., Aschengrau, A. 2002. A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res. Treat.* 75, 181-184.

Lash, T.L., Aschengrau, A. 1999. Active and passive cigarette smoking and the occurrence of breast cancer. *Am. J Epidemiol.* 149, 5-12.

LaVoie, E.J., Stern, S.L., Choi, C.I., Reinhardt, J., Adams, J.D. 1987. Transfer of the tobacco-specific carcinogens N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and benzo[a]pyrene into the milk of lactating rats. *Carcinogenesis* 8, 433-437.

- Lawlor, D.A., Ebrahim, S., Smith, G.D. 2004. Smoking before the birth of a first child is not associated with increased risk of breast cancer: findings from the British Women's Heart and Health Cohort Study and a meta-analysis. *Br. J. Cancer* 91, 512-518.
- Les Etudes de Marche Createc. *Effects of Modified Packaging through Increasing the Size of Warnings on Cigarette Packages*. 2008.
- Li, C.I., Malone, K.E., Daling, J.R. 2005. The relationship between various measures of cigarette smoking and risk of breast cancer among older women 65-79 years of age (United States). *Cancer Causes Control* 16, 975-985.
- Li, D., Wang, M., Dhingra, K., Hittelman, W.N. 1996. Aromatic DNA adducts in adjacent tissues of breast cancer patients: clues to breast cancer etiology. *Cancer Res.* 56, 287-293.
- Lissowska, J., Brinton, L.A., Garcia-Closas, M. 2007. Re: more data regarding the effects of passive smoking on breast cancer risk among younger women. *Int. J. Cancer* 120, 2517-2518.
- Lissowska, J., Brinton, L.A., Zatonski, W., Blair, A., Bardin-Mikolajczak, A., Peplonska, B., Sherman, M.E., Szeszenia-Dabrowska, N., Chanock, S., Garcia-Closas, M. 2006. Tobacco smoking, NAT2 acetylation genotype and breast cancer risk. *Int. J. Cancer* 119, 1961-1969.
- MacMahon, B., Trichopoulos, D., Cole, P., Brown, J. 1982. Cigarette smoking and urinary estrogens. *N. Engl. J. Med.* 307, 1062-1065.
- Magnusson, C., Wedren, S., Rosenberg, L.U. 2007. Cigarette smoking and breast cancer risk: a population-based study in Sweden. *Br. J. Cancer* 97, 1287-1290.
- Mann, G.J., Thorne, H., Balleine, R.L., Butow, P.N., Clarke, C.L., Edkins, E., Evans, G.M., Fereday, S., Haan, E., Gattas, M., Giles, G.G., Goldblatt, J., Hopper, J.L., Kirk, J., Leary, J.A., Lindeman, G., Niedermayr, E., Phillips, K.A., Picken, S., Pupo, G.M., Saunders, C., Scott, C.L., Spurdle, A.B., Suthers, G., Tucker, K., Chenevix-Trench, G. 2006. Analysis of cancer risk and BRCA1 and BRCA2 mutation prevalence in the kConFab familial breast cancer resource. *Breast Cancer Res.* 8, R12.
- Marcus, P.M., Newman, B., Millikan, R.C., Moorman, P.G., Baird, D.D., Qaqish, B. 2000. The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). *Cancer Causes Control* 11, 271-278.
- Martin, F.L., Cole, K.J., Weaver, G., Hong, G.S., Lam, B.C., Balaram, P., Grover, P.L., Phillips, D.H. 2001. Genotoxicity of human breast milk from different countries. *Mutagenesis* 16, 401-406.
- Mayberry, R.M., Branch, P.T. 1994. Breast cancer risk factors among Hispanic women. *Ethn. Dis.* 4, 41-46.
- Mechanic, L.E., Millikan, R.C., Player, J., de Cotret, A.R., Winkel, S., Worley, K., Heard, K., Heard, K., Tse, C.K., Keku, T. 2006. Polymorphisms in nucleotide excision repair genes, smoking and breast cancer in African Americans and whites: a population-based case-control study. *Carcinogenesis* 27, 1377-1385.
- Meijers-Heijboer, H., van, G.B., van Putten, W.L., Henzen-Logmans, S.C., Seynaeve, C., Menke-Pluymers, M.B., Bartels, C.C., Verhoog, L.C., van den Ouweland, A.M., Niermeijer, M.F., Brekelmans, C.T., Klijn, J.G. 2001. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N. Engl. J. Med.* 345, 159-164.
- Metsola, K., Kataja, V., Sillanpaa, P., Siivola, P., Heikinheimo, L., Eskelinen, M., Kosma, V.M., Uusitupa, M., Hirvonen, A., 2005. XRCC1 and XPD genetic polymorphisms, smoking and breast cancer risk in a Finnish case-control study. *Breast Cancer Res.* 7, R987-R997.
- Michnovicz, J.J., Hershcopf, R.J., Naganuma, H., Bradlow, H.L., Fishman, J. 1986. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *N. Engl. J. Med.* 315, 1305-1309.
- Miller, M.D., Marty, M.A., Broadwin, R., Johnson, K.C., Salmon, A.G., Winder, B., Steinmaus, C. 2007. The association between exposure to environmental tobacco smoke and breast cancer: a review by the California Environmental Protection Agency. *Prev. Med.* 44, 93-106.
- Millikan, R.C., Pittman, G.S., Newman, B., Tse, C.K., Selmin, O., Rockhill, B., Savitz, D., Moorman, P.G., Bell, D.A. 1998. Cigarette smoking, N-acetyltransferases 1 and 2, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 7, 371-378.

Expert Panel on Tobacco Smoke and Breast Cancer Risk

- Morabia, A., Bernstein, M., Heritier, S. 1998. Re: Hunter, D.J., Hankinson, S.E., Hough, H. et al. (1997), A prospective study of NAT2 acetylation genotype, cigarette smoking and risk of breast cancer. *Carcinogenesis*, 18, 2127-2132
- Morabia, A. 2002. Smoking (active and passive) and breast cancer: epidemiologic evidence up to June 2001. *Environ. Mol. Mutagen.* 39, 89-95.
- Morabia, A., Bernstein, M., Heritier, S., Khatchatrian, N. 1996. Relation of breast cancer with passive and active exposure to tobacco smoke. *Am. J Epidemiol.* 143, 918-928.
- Morabia, A., Lash, T.L., Aschengrau, A. 2001. Passive cigarette smoking and breast cancer. Environmental Tobacco Smoke. In: Ed: Watson RR, Witten ML (Eds), *Environmental Tobacco Smoke*. CRC Press, Boca Raton, pp. 177-193.
- Naito, S., Tanaka, K., Koga, H., Kotoh, S., Hirohata, T., Kumazawa, J. 1995. Cancer occurrence among dyestuff workers exposed to aromatic amines. A long term follow-up study. *Cancer* 76, 1445-1452.
- Nkondjock, A., Robidoux, A., Paredes, Y., Narod, S.A., Ghadirian, P. 2006. Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians. *Breast Cancer Res. Treat.* 98, 285-294.
- Office of Research and Development, U.E., 2002. *Respiratory health effects of passive smoking: Lung cancer and other disorders*. US EPA, Washington, D.C.
- Olson, J.E., Vachon, C.M., Vierkant, R.A., Sweeney, C., Limburg, P.J., Cerhan, J.R., Sellers, T.A. 2005. Prepregnancy exposure to cigarette smoking and subsequent risk of postmenopausal breast cancer. *Mayo Clin. Proc.* 80, 1423-1428.
- Palmer, J.R., Rosenberg, L., 1993. Cigarette smoking and the risk of breast cancer. *Epidemiol. Rev.* 15, 145-156.
- Palmer, J.R., Rosenberg, L., Clarke, E.A., Stolley, P.D., Warshauer, M.E., Zauber, A.G., Shapiro, S. 1991. Breast cancer and cigarette smoking: a hypothesis. *Am. J Epidemiol.* 134, 1-13.
- Parkin, D.M., Pisani, P., Ferlay, J. 1999. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int. J Cancer* 80, 827-841.
- Pawlega, J. 1992. Breast cancer and smoking, vodka drinking and dietary habits. A case-control study. *Acta Oncol.* 31, 387-392.
- Perera, F.P., Estabrook, A., Hewer, A., Channing, K., Rundle, A., Mooney, L.A., Whyatt, R., Phillips, D.H. 1995. Carcinogen-DNA adducts in human breast tissue. *Cancer Epidemiol. Biomarkers Prev.* 4, 233-238.
- Phillips D.H., Martin F.L., Grover P.L., Williams J.A., 2001. Toxicological basis for a possible association of breast cancer with smoking and other sources of environmental carcinogens. *J Women's Cancer* 3, 9-16.
- Physicians for a Smoke-Free Canada. *Smoking Prevalence 1965 - 2006*. Factsheet, <http://www.smoke-free.ca/factsheets/pdf/prevalence.pdf> (accessed March 19, 2009). 2008.
- Prescott, J., Ma, H., Bernstein, L., Ursin, G. 2007. Cigarette smoking is not associated with breast cancer risk in young women. *Cancer Epidemiol. Biomarkers Prev.* 16, 620-622.
- Rautalahti, M., Albanes, D., Virtamo, J., Palmgren, J., Haukka, J., Heinonen, O.P. 1993. Lifetime menstrual activity--indicator of breast cancer risk. *Eur. J Epidemiol.* 9, 17-25.
- Rehm, J., Baliunas, D., Brochu, B., Fisher, B., Gnam, W., Patra, J., Popova, S., Sarnocinska-Hart, A., Taylor, B. *The Costs of Substance Abuse in Canada 2002*. 2006. Ottawa, Canada, Canadian Centre on Substance Abuse.
- Repace J.L. 2006. Exposure to Secondhand Smoke. In: W Ott, A Steinemann, L Wallace (Eds), *Exposure Analysis*. CRC Press.
- Reynolds, P., Hurley, S., Goldberg, D. 2006. Re: Accumulating evidence on passive and active smoking and breast cancer risk. *Int J Cancer* 119, 239.
- Reynolds, P., Hurley, S., Goldberg, D.E., Anton-Culver, H., Bernstein, L., Deapen, D., Horn-Ross, P.L., Peel, D., Pinder, R., Ross, R.K., West, D., Wright, W.E., Ziogas, A. 2004. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J. Natl. Cancer Inst.* 96, 29-37.

- Rockhill, B., Weinberg CR, Newman, B., 1998. Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability. *Am J of Epidemiol* 147, 826-833.
- Roddam, A.W., Pirie, K., Pike, M.C., Chilvers, C., Crossley, B., Hermon, C., McPherson, K., Peto, J., Vessey, M., Beral, V. 2007. Active and passive smoking and the risk of breast cancer in women aged 36-45 years: a population based case-control study in the UK. *Br. J. Cancer* 97, 434-439.
- Rohan, T.E., Baron, J.A. 1989. Cigarette smoking and breast cancer. *Am. J Epidemiol.* 129, 36-42.
- Rollison, D.E., Brownson, R.C., Hathcock, H.L., Newschaffer, C.J. 2008. Case-control study of tobacco smoke exposure and breast cancer risk in Delaware. *BMC. Cancer* 8, 157.
- Rosenberg, M.S. 2005. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. *Evolution* 59, 464-468.
- Russo, I.H. 2002. Cigarette smoking and risk of breast cancer in women. *Lancet* 360, 1033-1034.
- Russo, I.H., Russo, J. 1993. Physiological bases of breast cancer prevention. *Eur. J Cancer Prev.* 2 Suppl 3, 101-111.
- Russo, J., Russo, I.H. 1980. Influence of differentiation and cell kinetics on the susceptibility of the rat mammary gland to carcinogenesis. *Cancer Res.* 40, 2677-2687.
- Schechter, M.T., Miller, A.B., Howe, G.R. 1985. Cigarette smoking and breast cancer: a case-control study of screening program participants. *Am. J Epidemiol.* 121, 479-487.
- Schechter, M.T., Miller, A.B., Howe, G.R., Baines, C.J., Craib, K.J., Wall, C. 1989. Cigarette smoking and breast cancer: case-control studies of prevalent and incident cancer in the Canadian National Breast Screening Study. *Am. J Epidemiol.* 130, 213-220.
- Schick, S., Glantz, S.A. 2005. Philip Morris toxicological experiments with fresh sidestream smoke: more toxic than mainstream smoke. *Tob. Control* 14, 396-404.
- Schick, S., Glantz, S.A. 2006. Sidestream cigarette smoke toxicity increases with aging and exposure duration 4. *Tob. Control* 15, 424-429.
- Sillanpaa, P., Hirvonen, A., Kataja, V., Eskelinen, M., Kosma, V.M., Uusitupa, M., Vainio, H., Mitrunen, K. 2005. NAT2 slow acetylator genotype as an important modifier of breast cancer risk. *Int. J. Cancer* 114, 579-584.
- Slattery, M.L., Curtin, K., Giuliano, A.R., Sweeney, C., Baumgartner, R., Edwards, S., Wolff, R.K., Baumgartner, K.B., Byers, T. 2008. Active and passive smoking, IL6, ESR1, and breast cancer risk. *Breast Cancer Res. Treat.* 109, 101-111.
- Smith, S.J., Deacon, J.M., Chilvers, C.E. UK National Case-Control Study Group, 1994. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br. J Cancer* 70, 112-119.
- Somogyi, A., Beck, H. 1993. Nurturing and breast-feeding: exposure to chemicals in breast milk. *Environ. Health Perspect.* 101 Suppl 2, 45-52.
- Stroup, N.E., Layde, P.M., Webster, L.A., Wingo, P.A., Rubin, G.L., Ory, H.W. The Canadian and Steroid Hormone Study Group. Cigarette smoking and breast cancer. L.Rosenberg. *Smoking and Reproductive Health.* 167-172. 1987. Littleton, MA, PSG Publisher.
- Struewing, J.P., Hartge, P., Wacholder, S., Baker, S.M., Berlin, M., McAdams, M., Timmerman, M.M., Brody, L.C., Tucker, M.A. 1997. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N. Engl. J. Med.* 336, 1401-1408.
- Suzuki, T., Matsuo, K., Wakai, K., Hiraki, A., Hirose, K., Sato, S., Ueda, R., Tajima, K. 2007. Effect of familial history and smoking on common cancer risks in Japan. *Cancer* 109, 2116-2123.
- Swaminathan, S., Frederickson, S.M., Hatcher, J.F. 1994. Metabolic activation of N-hydroxy-4-acetylamino-biphenyl by cultured human breast epithelial cell line MCF 10A. *Carcinogenesis* 15, 611-617.

Terry, P.D., Goodman, M. 2006. Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 15, 602-611.

Terry, P.D., Miller, A.B., Rohan, T.E., 2002. Cigarette smoking and breast cancer risk: a long latency period? *Int. J Cancer* 100, 723-728.

Terry, P.D., Rohan, T.E., 2002. Cigarette smoking and the risk of breast cancer in women: A review of the literature. *Cancer Epidemiol. Biomarkers Prev.* 11, 953-971.

Thompson, P.A., DeMarini, D.M., Kadlubar, F.F., McClure, G.Y., Brooks, L.R., Green, B.L., Fares, M.Y., Stone, A., Josephy, P.D., Ambrosone, C.B. 2002. Evidence for the presence of mutagenic arylamines in human breast milk and DNA adducts in exfoliated breast ductal epithelial cells. *Environ. Mol. Mutagen.* 39, 134-142.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General.* 2004. Atlanta, GA: U.S. Department of Health and Human Services.

U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General.* 2006. Atlanta, GA.

U.S. Department of Health and Human Services, *P.H.S.N.T.P. Report on Carcinogens*, Tenth Edition. 2002.

van der Hel, O.L., Peeters, P.H., Hein, D.W., Doll, M.A., Grobbee, D.E., Kromhout, D., Bueno de Mesquita, H.B. 2003. NAT2 slow acetylation and GSTM1 null genotypes may increase postmenopausal breast cancer risk in long-term smoking women. *Pharmacogenetics* 13, 399-407.

Vineis, P., Bartsch, H., Caporaso, N., Harrington, A.M., Kadlubar, F.F., Landi, M.T., Malaveille, C., Shields, P.G., Skipper, P., Talaska, G. 1994. Genetically based N-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. *Nature* 369, 154-156.

Vineis, P., McMichael, A., 1996. Interplay between heterocyclic amines in cooked meat and metabolic phenotype in the etiology of colon cancer. *Cancer Causes Control* 7, 479-486.

Wacholder, S., Rothman, N., Caporaso, N. 2000. Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. *J Natl. Cancer Inst.* 92, 1151-1158.

Wartenberg, D., Calle, E.E., Thun, M.J., Heath, C.W., Jr., Lally, C., Woodruff, T. 2000. Passive smoking exposure and female breast cancer mortality. *J Natl. Cancer Inst.* 92, 1666-1673.

World Health Organization. *First Meeting of the Working Group on the WHO Framework Convention on Tobacco Control: Economics of Tobacco Control.* 1999. Geneva, Switzerland.

World Health Organization. *WHO Framework Convention on Tobacco Control, Article 12.* 2005. Geneva, Switzerland.

Zheng, T., Holford, T.R., Zahm, S.H., Owens, P.H., Boyle, P., Zhang, Y., Wise, J.P., Sr., Stephenson, L.P., Ali-Osman, F. 2002. Cigarette smoking, glutathione-S-transferase M1 and t1 genetic polymorphisms, and breast cancer risk (United States). *Cancer Causes Control* 13, 637-645.

Appendix 1: Summary of Epidemiological Reviews and Meta-Analyses Assessing the Association between Breast Cancer and Tobacco Smoke, 1993-2008

Palmer, J.R., Rosenberg, L., 1993. Cigarette smoking and the risk of breast cancer. *Epidemiol. Rev.* 15, 145-156.

Conclusion/Paraphrased: It is unlikely that cigarette smoking has a net effect of reducing the risk of breast cancer. Apart from the early case-control groups, only a few studies have found an inverse association with smoking. Moreover, a strong link between estrogen activity and cigarette smoking, or between estrogen levels and breast cancer risk has not been demonstrated. There is also little evidence to suggest that cigarette smoking materially increases risk. Most studies have found no association or very small positive associations for ever smoking, current smoking, or heavy smoking (Conclusion). In total, 10 case-control and 5 cohort studies have been conducted. Estimates for the case-control studies ranged from 0.91 to 1.59, whereas the cohort studies ranged from 0.86 to 1.19 among the heaviest smoking categories.

Morabia, A., 2002. Smoking (active and passive) and breast cancer: epidemiologic evidence up to June 2001. *Environ. Mol. Mutagen.* 39, 89-95.

Authors' Summary: We synthesize the information – presented in a series of four reports – on the epidemiologic, toxicologic, endocrinologic, cellular and genomic bases for an association between smoking and breast cancer. The literature provides data supporting each of the steps of a theoretical model bridging cigarette smoke exposure to breast cancer: a) Tobacco smoking contains multiple potential carcinogens; b) These carcinogens can be activated into electrophilic intermediates by appropriate enzymes; c) Some of these enzymes have been found to be active in the breast epithelium; d) Interactions between these genes and smoking with respect to the breast cancer risk have been reported but not widely reproduced; e) Electrophilic intermediates of tobacco compounds bind to DNA to form DNA adducts that can be found in the mammary gland; f) Genomic alterations, such as microsatellite instability or loss of heterozygosity observed in vitro after exposure of HBEC to tobacco carcinogens resemble those seen in familial breast cancer. However, the literature does not show which of these steps are actually connected in a causal chain to breast cancer. In the future, there is need to better coordinate and integrate research activity of the various disciplines required to understand the pathophysiology of breast cancer.

Collaborative Group on Hormonal Factors in Breast Cancer, 2002. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br. J Cancer 87, 1234-1245.

Abstract: Alcohol and tobacco consumption are closely correlated and published results on their association with breast cancer have not always allowed adequately for confounding between these exposures. Over 80% of the relevant information worldwide on alcohol and tobacco consumption and breast cancer were collated, checked and analysed centrally. Analyses included 58 515 women with invasive breast cancer and 95 067 controls from 53 studies. Relative risks of breast cancer were estimated, after stratifying by study, age, parity and, where appropriate, women's age when their first child was born and consumption of alcohol and tobacco. The average consumption of alcohol reported by controls from developed countries was 6.0 g per day, i.e. about half a unit/drink of alcohol per day, and was greater in ever-smokers than never-smokers, (8.4 g per day and 5.0 g per day, respectively). Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 (1.19 – 1.45, P50.00001) for an intake of 35 – 44 g per day alcohol, and 1.46 (1.33 – 1.61, P50.00001) for 545 g per day alcohol. The relative risk of breast cancer increased by 7.1% (95% CI 5.5 – 8.7%; P50.00001) for each additional 10 g per day intake of alcohol, i.e. for each extra unit or drink of alcohol consumed on a daily basis. This increase was the same in ever smokers and never-smokers (7.1% per 10 g per day, P50.00001, in each group). By contrast, the relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. When analyses were restricted to 22 255 women with breast cancer and 40 832 controls who reported drinking no alcohol, smoking was not associated with breast cancer (compared to never-smokers, relative risk for ever-smokers=1.03, 95% CI 0.98 – 1.07, and for current smokers=0.99, 0.92 – 1.05). The results for alcohol and for tobacco did not vary substantially across studies, study designs, or according to 15 personal characteristics of the women; nor were the findings materially confounded by any of these factors. If the observed relationship for alcohol is causal, these results suggest that about 4% of the breast cancers in developed countries are attributable to alcohol. In developing countries, where alcohol consumption among controls averaged only 0.4 g per day, alcohol would have a negligible effect on the incidence of breast cancer. In conclusion, smoking has little or no independent effect on the risk of developing breast cancer; the effect of alcohol on breast cancer needs to be interpreted in the context of its beneficial effects, in moderation, on cardiovascular disease and its harmful effects on cirrhosis and cancers of the mouth, larynx, oesophagus and liver.

Terry, P.D., Rohan, T.E., 2002. Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol. Biomarkers Prev.* 11, 953-971.

Abstract: Animal experiments and *in vitro* studies have shown that compounds found in tobacco smoke, such as polycyclic hydrocarbons, aromatic amines, and *N*-nitrosamines, may induce mammary tumors. The findings of smoking specific DNA adducts and *p53* gene mutations in the breast tissue of smokers also support the biological plausibility of a positive association between cigarette smoking and breast cancer, as does the detection of carcinogenic activity in breast fluid. However, epidemiological studies conducted over the past few decades have variably shown positive, inverse, or null associations. To help reconcile the discrepant findings, epidemiologists have paid increasing attention to measures of exposure to tobacco smoke that might be of the greatest etiological importance, to aspects of the smoker that might modify the association between smoking and breast cancer risk, and to the potentially different associations that might exist with different types of breast tumors, such as those with and without estrogen or progesterone receptors. Overall, the results of these studies suggest that smoking probably does not decrease the risk and indeed suggest that there may be an increased breast cancer risk with smoking of long duration, smoking before a first full-term pregnancy, and passive smoking. These findings require confirmation in future studies, as do suggestions of increased risk among women with certain genotypes.

U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. 2004. Atlanta, GA: U.S. Department of Health and Human Services.

Chapter Summary: Since the 2001 Surgeon General's Report, IARC has concluded that the evidence is indicative of no association between smoking and breast cancer. The weight of epidemiological evidence supports the conclusion that smoking is not associated with breast cancer risk. Subgroups of women cannot yet be reliably identified who are at an increased risk of breast cancer because of smoking, compared with the general population of women. Whether women who are at a very high risk of breast cancer because of mutations in BRCA1 or BRCA2 genes can lower their risks by smoking has not been established. A Meta-RR of 1.03(SE =0.02) of breast cancer in ever smokers vs. never was found when combining cohort and case-control studies.

Alberg, A.J., Daudt, A., Huang, H.Y., Hoffman, S.C., Comstock, G.W., Helzlsouer, K.J., Strickland, P.T., Bell, D.A., 2004. N-acetyltransferase 2 (NAT2) genotypes, cigarette smoking, and the risk of breast cancer. *Cancer Detect. Prev.* 28, 187-193.

Discussion: Given the limited size of our current study, and the fact that a non-trivial proportion of participants were missing information concerning pack-years of smoking and exposure to passive smoking, chance remains a viable explanation for our findings that cigarette smoking was not associated with breast cancer risk. It is thus useful to compare the results of this study with eight investigations that examined the association between NAT2 genotypes, smoking, and breast cancer. When the crude results of the nine studies were pooled using the Mantel-Haenzsel odds ratio, which is weighted by study size, the OR between ever-versus-never smoking and breast cancer was 1.37 (95% CL 1.19-1.58) among slow acetylators, compared to 1.15 (95% CL 0.97-1.35) among rapid acetylators. Based on the 6 studies that could contribute data, cigarettes smoking was slightly more strongly associated with breast cancer risk among women with NAT2 slow acetylators genotypes if they were current smokers (OR 1.41; 95% CL 1.11-1.79) than former smokers (OR 1.27; 95% CL 1.01-1.60). Cigarette smoking was most strongly associated with breast cancer risk in postmenopausal women with the NAT2 slow acetylation genotype (OR 1.61; 95% CL 1.29-2.01), though comparisons were largely limited to ever-versus-never cigarette smokers. The present study together with other epidemiological studies provides at least modest support for the hypothesis that cigarette smoking is associated with an increased breast cancer risk in women with the NAT2 slow acetylator genotype.

Lawlor, D.A., Ebrahim, S., Smith, G.D., 2004. Smoking before the birth of a first child is not associated with increased risk of breast cancer: findings from the British Women's Heart and Health Cohort Study and a meta-analysis. *Br. J Cancer* 91, 512-518.

Abstract: It has been suggested that the period between puberty and first birth is a time when the breast is particularly susceptible to carcinogenic effects. In a cohort of 3047 women aged 60–79 years (N¼139 breast cancer cases), we found no association between smoking before the birth of a first child and breast cancer risk: fully adjusted (for age, number of children, age at birth of first child, age at menarche, age at menopausal, hysterectomy and/or oophorectomy, ever use of oral contraception, use of hormone replacement therapy, alcohol consumption, body mass index, childhood and adulthood social class) odds ratio 1.06 (95% CI: 0.72, 1.56). The pooled estimate from a meta-analysis of our study and 11 previously published studies (N¼6528 cases) was 1.07 (0.94, 1.22). We conclude that smoking prior to the birth of a first child is not associated with increased risk of breast cancer.

International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco Smoke and Involuntary Smoking. 2004. Lyon.

Part of the Introduction: Thirty-six case-control studies and eight cohort studies as well as one large pooled analysis of data from 10 cohort and 29 case-control studies from the Collaborative Group on Hormonal Factors in Breast Cancer Study (2002) were examined to assess the relationship between smoking and breast cancer risk. The Oxford Collaborative Study included over 80% of the worldwide epidemiological data on breast cancer and on alcohol and tobacco consumption. The analysis, which examined the relationship between smoking and breast cancer, and found it to be substantially confounded by the effect of alcohol consumption, and not substantially confounded by any other factors. When the analyses were restricted to 22 255 cases and 40 832 controls who reported to drink no alcohol, smoking was not associated with breast cancer (compared with never-smokers, the RR for ever-smokers was 1.03 (95% CI, 0.98-1.07) and for current smokers was 0.99 (95% CI, 0.92-1.05).

Johnson, K.C., 2005. Accumulating evidence on passive and active smoking and breast cancer risk. *Int. J. Cancer* 117, 619-628.

Abstract: The aim of the study was to examine the risk of breast cancer associated with passive and active smoking and to explore risk heterogeneity among studies. Nineteen of 20 located published studies of passive smoking and breast cancer risk among women met basic quality criteria. Pooled relative risk estimates for breast cancer were calculated for 1) life-long non-smokers with regular passive exposure to tobacco smoke and 2) women who smoked. They were compared to women categorized as never regularly exposed to tobacco smoke. The pooled risk estimate for breast cancer associated with passive smoking among life-long non-smokers was 1.27 (95% CI (CI), 1.11–1.45). In the subset of 5 studies (all case-control studies) with more complete exposure assessment (quantitative long-term information on the 3 major sources of passive smoke exposure: childhood, adult residential and occupational), the pooled risk estimate for exposed non-smokers was 1.90 (95%CI, 1.53–2.37). For the 14 studies with less complete passive exposure measures the risk was 1.08 (95%CI, 0.99–1.19) overall, 1.16 for 7 case-control and 1.06 for 7 cohort studies, although dose-response results in 3 of 4 Asian cohort studies suggested increased risk. The overall premenopausal breast cancer risk associated with passive smoking among life-long non-smokers was 1.68 (95%CI 1.33–2.12), and 2.19 (95% CI 1.68–2.84) for the 5 of 14 studies with more complete exposure assessment. For women who had smoked the breast cancer risk estimate was 1.46 (95%CI 1.15–1.85) when compared to women with neither active nor regular passive smoke exposure; 2.08 (95% CI 1.44–3.01) for more complete and 1.15 (95% CI 0.92–1.43) for less complete passive exposure assessment. Studies with thorough passive smoking exposure assessment implicate passive and active smoking as risk factors for premenopausal breast cancer. Cohort studies with thorough passive smoking assessment would be helpful and studies exploring biological mechanisms are needed to explain the unexpected similarity of the passive and active risks.

California Environmental Protection Agency. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant <http://www.arb.ca.gov/regact/ets2006/ets2006.htm> (accessed 25-03-2009). 2005.

Specific Findings and Conclusions: The weight of evidence (including toxicology of ETS constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women. A pooled risk estimate of 1.68 is derived in the meta-analysis among this subgroup, and when restricted to the studies with better exposure assessment, an estimate of 2.20 is obtained. These pooled estimates correspond to an approximate 68-120% increased breast cancer risk. In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause, risk estimates cluster around a null association. There are, however, elevated risk estimates in some studies for older/postmenopausal women either overall or in specific strata. The evidence to date for older/postmenopausal women is, therefore, considered inconclusive. Further research indicating a positive association would be necessary prior to altering this finding. An overall summary risk estimate from the meta-analysis of 19 studies among women of all ages was 1.25 (95% CI 1.08-1.44).

U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General <http://www.surgeongeneral.gov/library/secondhandsmoke/> (accessed 25-03-2009). 2006. Atlanta, GA.

Chapter Summary: The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer. Findings from prospective cohort studies and case-control studies differ to an extent that cannot plausibly be explained by differences in the quality of exposure measurements. The positive association is largely observed in case-control studies among women with premenopausal breast cancer. While greater susceptibility to tobacco smoke carcinogens during adolescence or at an early age has been hypothesized, there is still considerable uncertainty as to why secondhand smoke would only affect risk for premenopausal breast cancer. The overall pooled estimate is elevated, but the elevation largely comes from the increased risks estimated for premenopausal women in selected case-control studies. An overall pooled risk estimate of 1.20 (95% CI 0.92-1.13) was obtained from the 7 prospective cohort studies, whereas the 14 case-control studies resulted in a pooled risk estimate of 1.40 (95% CI 1.17-1.67). With regard to biologic plausibility, involuntary smoking would be expected to expose breast tissue to the carcinogens in secondhand smoke, as would active smoking. However, the evidence that active smoking causes no overall increase in breast cancer risks weighs against a causal role for involuntary smoking

Terry, P.D., Goodman, M., 2006. Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 15, 602-611.

Abstract: Epidemiologic studies have examined the association between cigarette smoking and breast cancer risk according to genotype with increasing frequency, commensurate with the growing awareness of the roles genes play in detoxifying or activating chemicals found in cigarette smoke and in preventing or repairing the damage caused by those compounds. To date, 50 epidemiologic studies have examined the association between smoking and breast cancer risk according to variation in genes related to carcinogen metabolism, modulation of oxidative damage, and DNA repair.

Some of the findings presented here suggest possible effect modification by genotype. In particular, 14 epidemiologic studies have tended to show positive associations with long-term smoking among NAT2 slow acetylators, especially among postmenopausal women. Summary analyses produced overall meta-relative risk (RR) estimates for smoking of 1.2 [95% CI (95% CI), 1.0-1.5] for rapid acetylators and 1.5 (95% CI, 1.2-1.8) for slow acetylators. After stratification by menopausal status, the meta-RR for postmenopausal slow acetylators was 2.4 (95% CI, 1.7-3.3), whereas similar analyses for the other categories showed no association. In addition, summary analyses produced meta-RRs for smoking of 1.1 (95% CI, 0.8-1.4) when GSTM1 was present and 1.5 (95% CI, 1.1-2.1) when the gene was deleted. Overall, however, interpretation of the available literature is complicated by methodological limitations, including small sample sizes, varying definitions of smoking, and difficulties involving single nucleotide polymorphism selection, which likely have contributed to the inconsistent findings. These methodological issues should be addressed in future studies to help clarify the association between smoking and breast cancer.

Nagata, C., Mizoue, T., Tanaka, K., Tsuji, I., Wakai, K., Inoue, M., Tsugane, S., 2006. Tobacco smoking and breast cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn. J Clin. Oncol.* 36, 387-394.

Paraphrased from Results: A review was conducted to assess the association between smoking and breast cancer incidence or mortality among the Japanese population. A Medline search identified 3 cohorts and 8 case-control studies from 1966-2005. The relative risk (RR) or odds ratio (OR) of breast cancer for current smokers ranged from 0.71 to 6.26 in these studies. A significant increased risk among current smokers compared with never smokers (RR=1.7; 95% CI 1.0-3.1) was reported in one of the three cohort studies. Moderate to strong associations between smoking and breast cancer risk (OR>2.0) were observed in four of the eight case-control studies. Experimental studies have supported the biological plausibility of a positive association between tobacco smoking and breast cancer risk. The authors concluded that tobacco smoking possibly increases the risk of breast cancer in the Japanese population.

Miller, M.D., Marty, M.A., Broadwin, R., Johnson, K.C., Salmon, A.G., Winder, B., Steinmaus, C., 2007. The association between exposure to environmental tobacco smoke and breast cancer: a review by the California Environmental Protection Agency. *Prev. Med.* 44, 93-106.

Summary: Background: The California Environmental Protection Agency (Cal/EPA) recently completed a health effects assessment of exposure to environmental tobacco smoke (ETS) which resulted in California listing ETS as a Toxic Air Contaminant in January 2006. As part of the assessment, studies on the association between exposure to ETS and breast cancer were reviewed.

Methods: Twenty-six published reports (including 3 meta-analyses) evaluating the association between ETS exposure and breast cancer were reviewed. A weight-of-evidence approach was applied to evaluate the data and draw conclusions about the association between breast cancer and ETS exposure.

Results: The published data indicate an association between ETS and breast cancer in younger primarily premenopausal women. Thirteen of 14 studies (10 case-control and four cohort) that allowed analysis by menopausal status reported elevated risk estimates for breast cancer in premenopausal women, seven of which were statistically significant. Our meta-analyses indicated elevated summary relative risks ranging from OR 1.68 (95% C.I. 1.31-2.15) for all 14 studies to 2.20 (95% C.I. 1.69, 2.87) for those with the best exposure assessment.

Conclusions: Cal/EPA concluded that regular ETS exposure is causally related to breast cancer diagnosed in younger, primarily premenopausal women and that the association is not likely explained by bias or confounding.

Ambrosone, C.B., Kropp, S., Yang, J., Yao, S., Shields, P.G., Chang-Claude, J., 2008. Cigarette smoking, N-acetyltransferase 2 genotypes, and breast cancer risk: pooled analysis and meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 17, 15-26.

Abstract: Approximately 10 years ago, it was noted that smoking increased risk of breast cancer among women with N-acetyltransferase 2 (NAT2) slow acetylation genotypes. This report was followed by a number of studies to address this question. We pooled data from 10 existing studies and also conducted a meta-analysis of 13 studies published from 1996 to October 2006 that were conducted among women, were published in English, and had adequate information on smoking and NAT2 genotyping. Raw data were requested from authors. Unconditional logistic regression was done for pooled analysis, and random effect models was done for meta-analysis. Study heterogeneity was assessed, and sensitivity tests were done when subgroups were excluded from the analysis. In the pooled analysis, there was a significant interaction between smoking, NAT2 genotype, and risk of breast cancer [pack-

years (continuous variable, interaction = 0.03)], with higher pack-years significantly associated with an increased risk of breast cancer among women with NAT2 slow genotypes (pooled analysis relative risk, 1.49; 95% CI, 1.08-2.04). These findings were supported by the meta-analysis including all studies; pack-years were significantly associated with risk among slow acetylators in a dose-dependent fashion (meta-analysis relative risk, 1.44; 95% CI, 1.23-1.68 for ≥ 20 pack-years versus never smokers), but not among rapid acetylators. Similar relationships were noted for smoking status (ever, never) and duration of smoking. Our results show that cigarette smoking is associated with an increase in breast cancer risk among women with NAT2 slow acetylation genotypes. Because slow NAT2 genotypes are present in 50% to 60% of Caucasian populations, smoking is likely to play an important role in breast cancer etiology.