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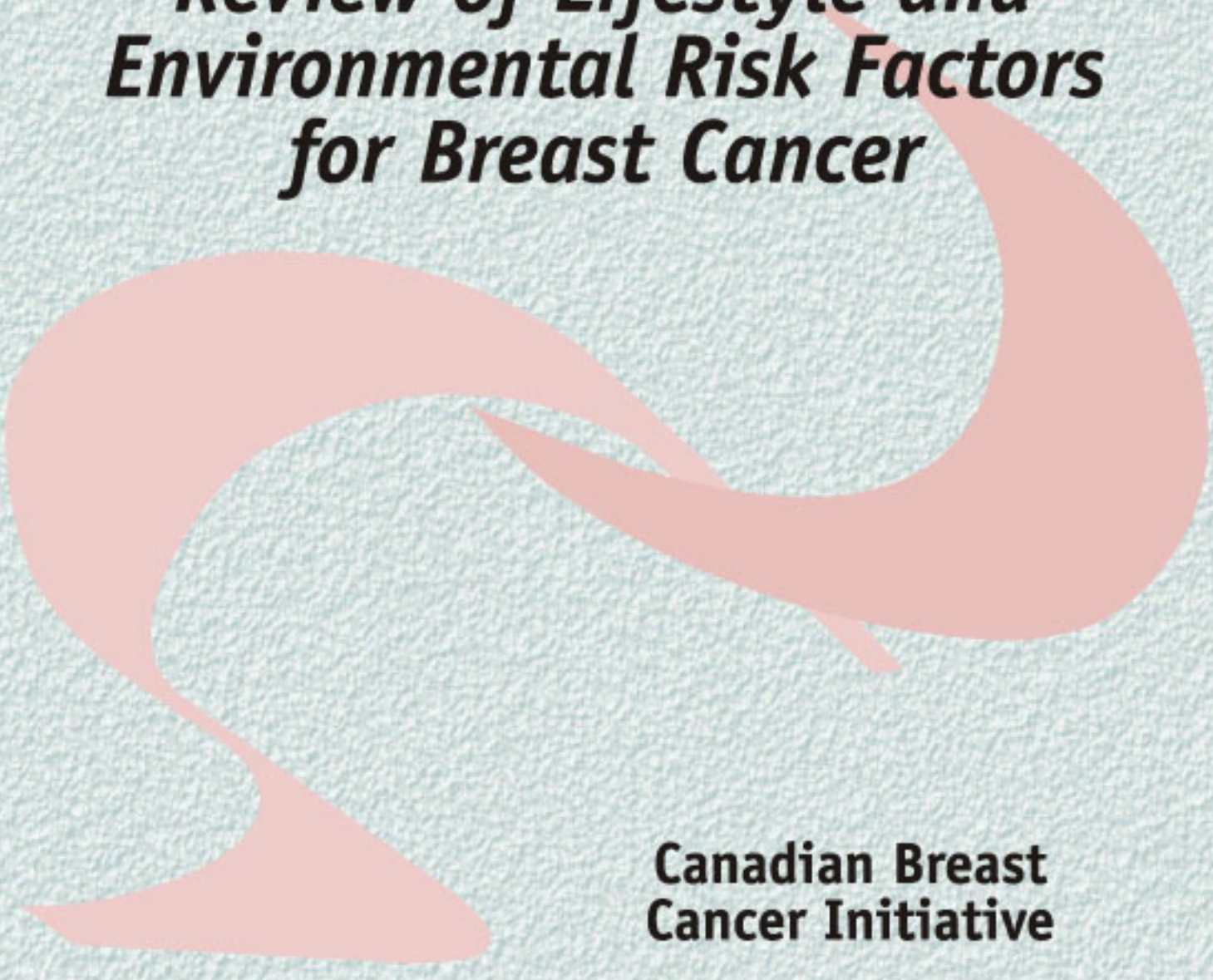
SUMMARY REPORT

Review of Lifestyle and Environmental Risk Factors for Breast Cancer



Canadian Breast Cancer Initiative

Canada

Summary Report

Review of Lifestyle and Environmental Risk Factors for Breast Cancer

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Report of the Working Group on Primary Prevention of Breast Cancer

Canadian Breast Cancer Initiative

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Health Canada

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CONTENTS

INTRODUCTION

Anastasia Chyz, MA, Janet Faith, MSc, Christine Friedenreich, PhD, Mark Goldberg, PhD, Sarah Lenz, MSc

This report summarizes 11 literature reviews completed by members of the Canadian Breast Cancer Initiative Working Group on Primary Prevention of Breast Cancer. These reviews were prepared in response to concern about the possible association between breast cancer and potentially modifiable risk factors such as diet and exposure to specific chemicals. Members of the Working Group reviewed the scientific literature and outlined their findings and recommendations in *Review of Lifestyle and Environmental Risk Factors for Breast Cancer*. The literature reviews were written in order to

- summarize the scientific evidence for the associations between selected modifiable risk factors and breast cancer
- identify gaps in current understanding regarding these relationships
- highlight the biological mechanisms that might be operative if these associations are indeed causal
- provide recommendations for future epidemiological and related interdisciplinary research.

Each author or group of authors focused on one of the following topics:

- Diet
- Alcohol consumption
- Anthropometric factors
- Physical activity
- Active smoking and exposure to environmental tobacco smoke
- Occupational exposures
- Electromagnetic field exposure
- Organochlorines
- Emerging hypotheses and methodological approaches
- Biological mechanisms for breast cancer
- Evolutionary etiology of breast cancer

This introductory section describes the work of the Canadian Breast Cancer Initiative and the Working Group; it also provides an overview of breast cancer in Canada and the world. The body of the Summary Report contains a summary of each literature review completed, and the concluding section describes the Working Group's recommendations, which are listed with each summary and in the Appendix.

The Canadian Breast Cancer Initiative

Breast cancer is the most frequently diagnosed cancer among Canadian women. Early in the year 2000, estimates suggested that there would be 19 200 new cases and 5500 deaths from this disease.[1] Recognizing that breast cancer is an important health issue in need of a nationwide initiative, Health Canada established the Canadian Breast Cancer Initiative (CBCI) in 1993. The activities and programs of the CBCI are designed to

- reduce the incidence of breast cancer
- reduce mortality from breast cancer
- improve the quality of life of those affected by breast cancer.

Phase I

The need for a federal initiative in the area of breast cancer was brought to the forefront in 1992 with the publication of "Breast Cancer: Unanswered Questions," a report from the Standing Committee on Health and Welfare, Social Affairs, Seniors, and the Status of Women. The federal government responded to this report by launching Phase I (1993-1998) of the CBCI with a $25-million, 5-year commitment to support breast cancer research and other related activities. The government contributed $10 million to the Canadian Breast Cancer Research Initiative (CBCRI) and dedicated the remaining $15 million to the development and enhancement of program activities for clinical practice guidelines, breast cancer screening, information exchange pilot projects, and professional education.

Phase II

In 1998, the federal government recognized the need to continue building on the important work accomplished in the breast cancer programs and research of Phase I, and renewed its commitment to the CBCI for Phase II (1998-2003) with stable, ongoing funding of $7 million per year. In addition, the Medical Research Council, now the Canadian Institutes of Health Research (CIHR), agreed to contribute $2 million per year to the Canadian Breast Cancer Research Initiative over the same period.

The renewed CBCI represents a collaborative effort involving federal, provincial, and territorial governments, professional associations, non-governmental organizations, academic institutions, and community groups. Phase II involves an expansion of research and programs that will build on the products, services, and outcomes of Phase I, while incorporating the capacity to address gaps in knowledge and emerging issues related to breast cancer. During Phase II, the CBCI will focus on the following areas:

- Research on breast cancer
- Prevention, early detection, and screening
- Surveillance and monitoring
- Enhancement of high-quality approaches to diagnosis, treatment, and care
- Community capacity building
- Evaluation and coordination.

The Primary Prevention Working Group

In 2000 the CBCI established a Working Group on Primary Prevention of Breast Cancer to advise on the priority areas for research and prevention initiatives. In order to fulfill its mandate, the Working Group conducted a series of literature reviews on the association between breast cancer and factors possibly implicated in the etiology of the disease. Given that there are many possible risk factors that could be considered when dealing with primary prevention of breast cancer, the group decided to limit the scope of its work by focusing on *modifiable* risk factors, such as cigarette smoking, alcohol consumption, and occupational exposures. Much research has already been done on *non-modifiable* risk factors, such as menstrual history. Furthermore, when developing public health recommendations and population interventions, it is more appropriate to focus on behaviours and risk factors that individuals may be able to modify or that regulatory agencies may be able to control in some way (e.g., eliminating the use of carcinogenic chemicals in the workplace).

Note: An examination of the literature on chemoprevention of breast cancer was considered beyond the scope of the Working Group's mandate. Instead, the CBCI's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer and the Canadian Task Force on Preventive Health Care have undertaken an extensive review of the literature on chemoprevention, and jointly developed a clinical practice guideline on this topic. The guideline presents evidence and recommendations regarding the benefits and risks of chemoprevention of breast cancer with the estrogen modulators tamoxifen and raloxifene.[2]

Joint CBCI/CBCRI workshop on the primary prevention of breast cancer

The literature reviews that this report summarizes were prepared as background for a workshop on the primary prevention of breast cancer. The epidemiological evidence collected in *Review of Lifestyle and Environmental Risk Factors for Breast Cancer* will be the basis for discussion when a panel of invited scientists joins the Working Group members in delineating future steps for research in primary prevention of breast cancer.

This workshop will be held in Quebec City on May 3, 2001, before the second CBCRI *Reasons for Hope* scientific research conference. The CBCI and the CBCRI have convened this meeting with the following goal and objectives in mind:

Goal

To identify gaps in knowledge and research needs for breast cancer in women that will inform primary prevention research (excluding research about chemoprevention)

Objectives

- To evaluate scientific data regarding the etiology of breast cancer
- To provide recommendations for future research on modifiable risk factors with particular emphasis on lifestyle and environmental risk factors and the underlying biological mechanisms involved in the etiology of breast cancer

Overview of breast cancer in Canada and the world

Breast cancer is an important cause of morbidity and mortality among Canadian women. Current estimates suggest that 1 in 9.5 Canadian women will develop the disease during their lifetimes and 1 in 26 women will die from this cancer.[1]

Descriptive epidemiology of breast cancer

During the past 25 years, incidence rates in Canada have increased by approximately 28%. Rates have risen steadily, with minor fluctuations, between 1980 and 1999 (Figure 1).[3] The steepest increases were found in women over 50 years of age. The reasons for the increase in incidence rates are largely unknown, but early detection of breast cancer, mainly through mammography screening, may be a contributing factor.[4]

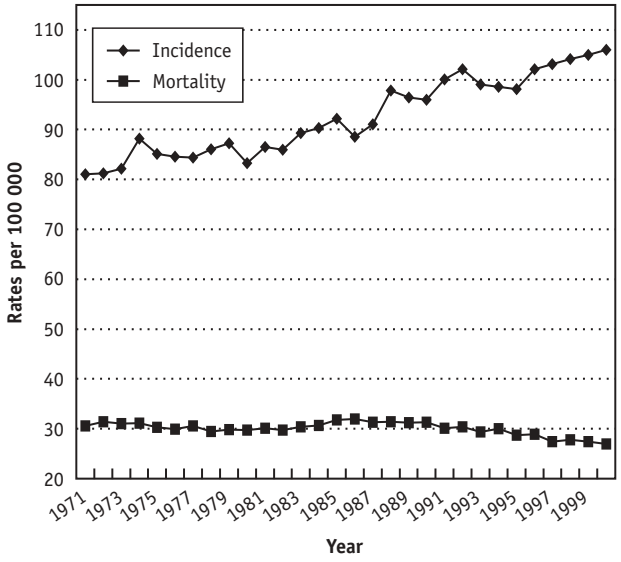
Age-standardized incidence rates by province vary considerably (Figure 2), with New Brunswick, Quebec, Newfoundland, Yukon, and the Northwest Territories showing the lowest rates, and British Columbia and Manitoba showing the highest. There is no clear reason for these regional differences, although different reporting practices may be a contributing factor.

There are also regional differences in mortality rates in Canada (Figure 3). Certain provinces with relatively low incidence rates have relatively high mortality rates (Nova Scotia, Quebec, Ontario), whereas other regions with relatively low incidence rates have similarly low mortality rates (Northwest Territories, Yukon).

On a global scale, the incidence of breast cancer appears to be greatest in more industrialized countries, the highest rates being found in Western Europe, the United States, and Canada (Figure 4).[5] The highest reported incidence rates are found among white women in the San Francisco Bay area, California (104.2 per 100 000), and the lowest are in The Gambia (3.4 per 100 000).[5]

Reasons for the international differences are unclear, but variations in registration practices or the way breast cancer is defined may be contributing factors. In addition, differences in risk factors for breast cancer (e.g., body weight, diet, endogenous hormone levels, and reproductive factors such as age at menarche, menstrual cycle length, parity, and lactation) may also play a role in these international differences.[5] Finally, the differences may relate to as yet unidentified environmental exposures.

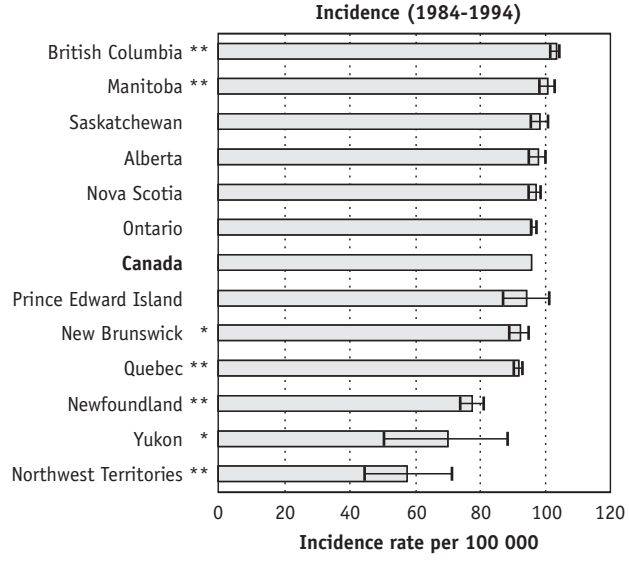
— Figure 1 —
Age-standardized incidence and mortality rates for breast cancer in Canada (rates are standardized to the age distribution of the 1991 Canadian population)



Note: Estimates of incidence rates are for the years 1996 and following, and estimates of mortality rates are for the years 1998 and following.

Source: *Canadian Cancer Statistics 2000*, Canadian Cancer Society, Toronto (http://www.cancer.ca).

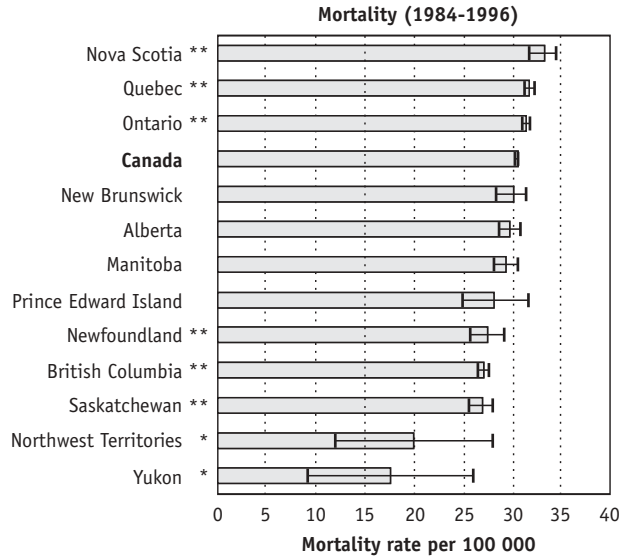
— Figure 2 —
Age-standardized breast cancer incidence per 100 000 women, by province and territory (rates are standardized to the age distribution of the 1991 Canadian population)



* p-value < 0.05
** p-value < 0.01

Source: *Cancer Updates: Breast Cancer in Canada*, Laboratory Centre for Disease Control, Health Canada, April 1999 (www.hc-sc.gc.ca/hpb/lcdc/publicat.html.).

— Figure 3 —
Age-standardized mortality rates from breast cancer, by province and territory (rates are standardized to the age distribution of the 1991 Canadian population)



* *p*-value < 0.05
** *p*-value < 0.01

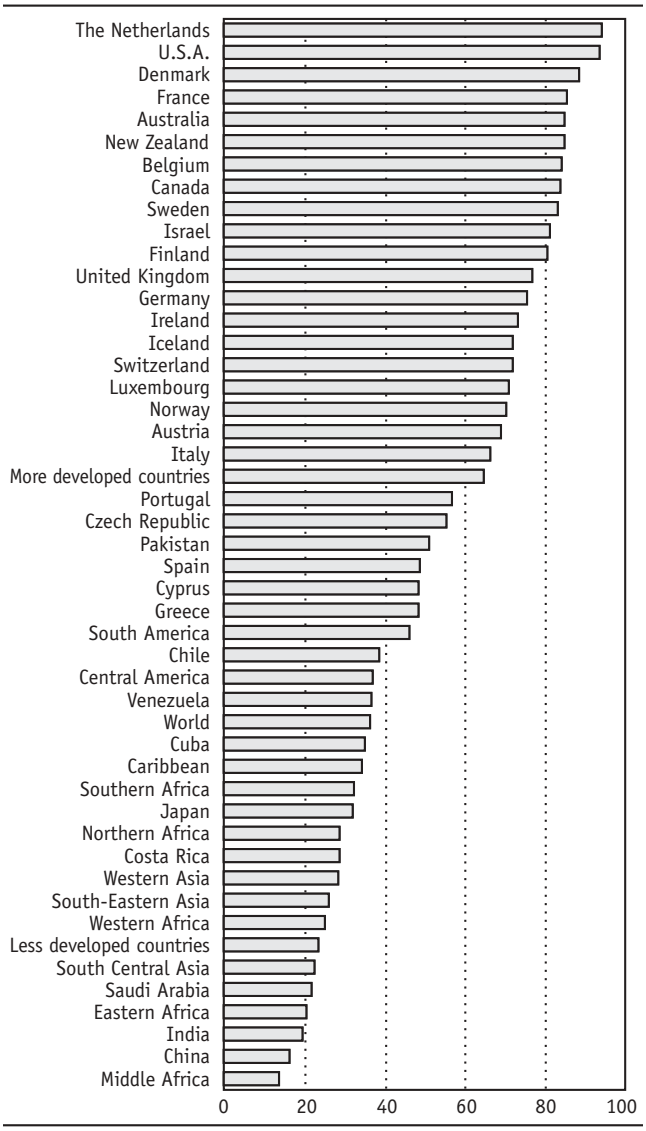
Source: *Cancer Updates: Breast Cancer in Canada*, Laboratory Centre for Disease Control, Health Canada, April 1999 (www.hc-sc.gc.ca/hpb/lcdc/publicat.html.).

Although worldwide incidence rates are increasing, mortality rates from breast cancer in Canada and Northern Europe are declining.[6,7] In contrast, there is a steady increase in breast cancer mortality in Japan,[8] even though incidence rates in Asia are much lower than in North America and Europe (Figure 4).

In the United States, mortality rates are declining among Caucasian women but not among women of other races.[9] In Portugal, Greece, Poland, Hungary, and Italy, mortality rates are still increasing.[10] These increases may be due in part to inequalities in health care in subpopulations and changes in society that affect reproductive, hormonal, and dietary risk factors. Additional contributors to increases in mortality may be poor early detection practices or inadequate management and treatment of breast cancer after diagnosis.[8]

There are good reasons to determine the causes of breast cancer and find preventive strategies. These reasons include the personal, familial, and societal burdens of the disease, and increased expenditures on health care.[11] The continuing increase in breast cancer incidence — only 25% to 40%[12] of which may be attributed to accepted risk factors—is yet another reason to determine the causes of this disease.[1]

— Figure 4 —
Breast cancer incidence rate by country (2000 estimates)



Source: *GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide*, International Agency for Research on Cancer, Lyon, France (www.iarc.fr).

Analytic epidemiology of breast cancer

Table 1 lists accepted and possible risk factors for breast cancer that are *not* being reviewed in this report.[9] The approximate relative risks associated with each factor are included.

As Table 1 indicates, the most significant risk factor for breast cancer is age, with incidence increasing significantly after age 50.[9] Family history of breast cancer is another very important risk factor: risks increase if a relative has had premenopausal bilateral breast cancer,

— Table 1 —
Summary of accepted and suspected risk factors for female breast cancer
not considered in *Review of Lifestyle and Environmental Risk Factors for Breast Cancer*

Risk factor	**Estimate of relative risk** (High risk/Low risk)
Accepted risk factors (relative risk greater than 4.0)	
Age	4-fold increase in risk (>50 years/<50 years)
Family history	
Relative with premenopausal bilateral breast cancer	> 4-fold increase in risk (Yes/No)
2 first-degree relatives with any form of breast cancer	> 4-fold increase in risk (Yes/No)
Country of birth	> 4-fold increase in risk (North America, Northern Europe/ Asia, Africa)
Benign proliferative breast disease	
Atypical hyperplasia	> 4-fold increase in risk (Yes/No)
Lobular carcinoma in situ	> 4-fold increase in risk (Yes/No)
Atypical epithelial cells in nipple aspirate fluid	> 4-fold increase in risk (Yes/No fluid produced)
Mutations in BRCA1 or BRCA2 genes, breast cancer at an early age	> 4-fold increase in risk (Yes/No)
Accepted risk factors (relative risk of 2.1-4.0)	
Chest irradiation (ionizing radiation)	2- to 4-fold increase in risk if exposure occurs from puberty through child-bearing years (High/Minimal)
Family history	
1 first-degree relative with any form of breast cancer	2- to 4-fold increase in risk (Yes/No)
Mammographically dense breast tissue	3- to 4-fold increase in risk (> 75%/fatty tissue)
Biopsy-confirmed benign proliferative breast disease	2- to 4-fold increase in risk (Yes/No)
Hyperplastic epithelial cells without atypia in nipple aspirate fluid	2- to 4-fold increase in risk (Yes/No fluid)
Accepted risk factors (relative risk of 1.1-2.0)	
Age at first full-term pregnancy	1.1- to 3-fold increase in risk (> 30 years/< 20 years)
Bilateral oophorectomy before age 40	1.1- to 3-fold increase in risk (No/Yes)
History of primary cancer of ovary or endometrium	1.1- to 2-fold increase in risk (Yes/No)
Socio-economic status (income, education)	1.1- to 2-fold increase (High/Low)
Marital status	1.1- to 2-fold increase in risk (Never married/Ever married)
Place of residence	1.1- to 2-fold increase in risk (Urban/Rural)
Race/ethnicity, breast cancer < 45 years of age	1.1- to 2-fold increase in risk (White/Hispanic, Asian)
Race/ethnicity, breast cancer < 40 years of age	1.1- to 2-fold increase in risk (Black/Hispanic, Asian)
Religion	1.1- to 2-fold increase in risk (Jewish/Seventh Day Adventist, Mormon)
Age at menopause	1.1- to 2-fold increase in risk (55/ 45)
Age at menarche	1.1- to 2-fold increase in risk (11/ 15)
Parity	1.1- to 3-fold increase in risk (Nulliparous/ Parous) Inconclusive after 1 child
Possible risk factors (all relative risk estimates less than 2.0)	
Hormone replacement therapy	Possible modest increase in risk, but restricted to women who took hormones for a long time or in high doses, or women > 60 years
Oral contraceptives	1.5-fold increase in risk (Current/Never). Increased risk for women with benign breast disease, women who used oral contraceptives at a late age (> 46-65), or women who used them very early (< 20 years) and/or before the first pregnancy
Breastfeeding	Suggestive of a protective effect, especially if breastfeeding occurs for a long period of time at a young age

or if two relatives have had any form of breast cancer.[13] Likewise, mutations in BRCA1 and BRCA2 genes substantially increase the risk of beast cancer, but the prevalence of these mutations appears to be low.[14] The risk of breast cancer is also increased by benign proliferative breast disease, particularly atypical hyperplasia,[9,15,16] and reproductive factors such as young age at menarche, greater age at first full-term pregnancy, and low parity.[9,15,16] Chest irradiation that occurs between puberty and childbearing years has also been shown to increase risk.[17] Factors such as high socio-economic status and marital status may also increase risk.[6,15,16] For some factors, such as hormone replacement therapy and oral contraceptive use,[18,19] there is inconclusive but suggestive evidence of an increase in risk, and for other factors, such as breast feeding,[20] the risk associations may be restricted to subgroups of the population (i.e., women diagnosed after age 50).

How topics were selected for *Review of Lifestyle and Environmental Risk Factors for Breast Cancer*

Before beginning the literature reviews that make up *Review of Lifestyle and Environmental Risk Factors for Breast Cancer*, the Working Group decided to concentrate on topics that could be classified as follows

- modifiable lifestyle and environmental risk factors for breast cancer
- new and emerging hypotheses for breast cancer etiology
- biological mechanisms and evolutionary aspects of breast cancer etiology.

The Working Group also decided that a full review of all breast cancer risk factors could not be conducted with the limited time and resources available, and that the authors of the literature reviews should attempt to identify areas of research in breast cancer etiology that might be particularly worthwhile.

Because 60% to 75% of breast cancers cannot be attributed to accepted and/or possible breast cancer risk factors, it is important to find out what can be done to prevent breast cancer from occurring in the first place. Research in areas that have not traditionally received adequate or complete attention may prove particularly valuable (see the Appendix for a list of the Working Group's research recommendations).

Summary of Literature Reviews

— CHAPTER 1 —
Review of Diet and Breast Cancer

Christine Friedenreich, PhD

This literature review explores the association between breast cancer and dietary intake. The author reviewed epidemiological literature published up to September 2000 after using the report of the World Cancer Research Fund/ American Institute for Cancer Research (WCRF/AICR) — *Food, Nutrition and Prevention of Cancer: A Global Perspective* — as the starting point for research up to 1996. The definitions for levels of scientific evidence developed by the WCRF/AICR panel were adopted for this literature review.

The review begins by describing the relevant epidemiological studies on the association between diet and breast cancer, then proceeds to discuss the biological mechanisms that are hypothesized regarding this association. After raising concerns about the methodological limitations of the studies, the review concludes with recommendations for future research.

Epidemiological studies

Most research attention on diet and breast cancer has been devoted to defining the etiologic role of dietary fat. At present, it appears that total fat *possibly* increases risk and that the risk increase is mainly attributable to saturated fats. Monounsaturated fats were found to *possibly* have no relation with breast cancer risk, with the exception of olive oil, which may confer a modest protective effect. Although polyunsaturated fats were found not to increase risk, different associations were found for specific polyunsaturated fatty acid subtypes.

Omega-3 fatty acids, found in fish oils, may decrease breast cancer risk, whereas omega-6 fatty acids, found in vegetable oils, appear to have no relation with breast cancer risk.

The data for protein and carbohydrate intakes and breast cancer were inconsistent, and no judgement is possible. There was a suggestion of an increased risk with animal protein intake and a possible decrease in risk for non-starch polysaccharides/dietary fibre intake.

More consistent evidence for associations with micronutrient intakes and breast cancer is available. Carotenoids, ß-carotene specifically, have been found to *possibly* decrease breast cancer risk and vitamin C intake may also decrease risk. No relation between breast cancer risk and retinol and vitamin E appears to exist, and there are some recent data that suggest a protective effect for total vitamin D, including intake from dietary, supplemental, and sunlight exposure sources. A possible protective effect of iodine and selenium has been hypothesized and has received preliminary investigation; however, the exact role of these elements in breast cancer etiology is still unclear.

Fairly consistent and strong evidence exists for a decreased risk of breast cancer with vegetable and fruit intake, with stronger risk reductions for vegetables. Meat intake possibly increases risk, poultry consumption is possibly not related to breast cancer risk, and fish intake may decrease risk. The data for milk and dairy products were too inconsistent to make a judgement. While preliminary evidence

for a protective effect exists for soy intake, the data are too sparse to make a judgement. The role of phytoestrogens, a major component of soy foods, is unknown, although preliminary indirect evidence does suggest a protective effect.

A high total caloric intake may increase breast cancer risk, since high-fat, energy-dense diets contribute to obesity, which is a risk factor for postmenopausal breast cancer. Calorie restriction is an established means of inhibiting tumorigenesis in animal models, and total energy intake is generally accepted as a modulator of carcinogenesis. The independent effects of dietary fat and total caloric intake have been difficult to assess despite the statistical methods that have been developed to adjust for energy intake.

Biological mechanisms

Numerous complex biological mechanisms have been postulated to explain how dietary factors can influence breast cancer risk, but none of these mechanisms has been confirmed. These hypothesized mechanisms include dietary effects on endogenous hormones and several metabolic, physiologic, and immune functions at both the initiation and promotion phases of carcinogenesis. Mechanisms specific to dietary fat, dietary fibre, vegetables and fruit, meat, and milk and dairy products are presented. Some initial intervention research is examining the effects of dietary change on endogenous hormone levels in an attempt to clarify the biological pathways whereby dietary fat might influence breast cancer risk. These studies are still preliminary and have methodological limitations.

Methodological limitations

Several methodological issues have influenced the results of diet and breast cancer studies. The primary methodological concern has been the measurement of dietary intake. These measurements are difficult, given the complex nature of dietary habits and the limited ability of questionnaires to assess the long-term intake of study subjects. Dietary assessment methods have generally focused on recent intakes, whereas the etiologically relevant time period for carcinogenesis may be in early life or at least several decades before cancer diagnosis. The influence of systematic and random measurement errors in dietary assessment methods has been examined, and methods to decrease the impact of these sources of error are being applied to recent and ongoing studies.

Diet and breast cancer studies have assessed risk associated with individual foods or nutrients rather than dietary patterns because they have used a "decompositional" rather than an "integrative" approach. Studies have also been limited by problems with confounding and collinearity, and a lack of consideration of subgroup effects. The dietary intakes of the study populations have often been too homogeneous, and this has decreased the ability to detect possible associations with breast cancer that may exist. The different methods for adjusting for total energy intake that have been developed and applied in epidemiological studies have resulted in inconsistencies across studies in the associations between dietary fat and breast cancer.

Future research

Gaps in our understanding of the association between breast cancer and diet might be filled with the help of the following:

- Improved dietary assessment methods
- Statistical methods that address measurement errors
- Observational and intervention studies that use more biological markers of long-term dietary exposure
- Observational, epidemiological studies that concentrate on measuring early life exposures and dietary patterns
- Observational epidemiological studies that (1) include ethnic and racial minorities, (2) examine effect modification and control for confounding, and (3) investigate more nutrient subtypes (e.g., dietary fatty acids)
- Intervention trials of specific dietary changes and intermediate and long-term endpoints
- More research on the underlying biological mechanisms that may be operative.

— CHAPTER 2 —
The Association Between Breast Cancer and Alcohol Consumption

Mark Goldberg, PhD, Sarah Lenz, MSc,
Sally Campbell, MSc, Marie-France Valois, MSc

This literature review explores the association between breast cancer and alcohol consumption. The authors reviewed epidemiological studies published in English or French between 1966 and 1999.

The review begins by describing the studies and proceeds to analyze the results and make recommendations for future research. (The results of each study are summarized in tabular form at the end of the original review.)

Epidemiological studies

A total of 59 case-control studies and 19 cohort studies were reviewed. In attempting to develop a metric for alcohol consumption, the authors found that the most common indices reported in the case-control studies (~90% of studies) were "recent" or "current" total alcohol consumption; in the cohort studies "usual" alcohol consumption was used exclusively. The authors deemed that a study showed that the risk of breast cancer was elevated if the estimated relative risk for this index met one of the following conditions:

There was evidence of a monotonic increase in risk by consumption—usually if the test for linear trend was statistically significant (p value < 0.05).

The 95% confidence limits associated with the odds ratio or relative risk for the categories of highest consumption when compared with the lowest category excluded unity.

Results

All told, 30% of studies of premenopausal women were positive (i.e. showed an elevated risk of breast cancer); 34% of studies of postmenopausal women were positive; and 54% of studies of pre- and postmenopausal women combined were positive. Differences were found in the proportion of positive studies by type of study. Ignoring distinctions by menopausal status and combining results across all types of analyses, the authors found that 13 of 19 cohort studies showed positive findings (68%; 95% confidence interval: 43%-87%), compared with 29 of 59 case-control studies (49%; 95% confidence interval: 36%-63%).

Overall, the proportion of positive studies (56%) was only slightly above what one would expect by chance. However, because of the small number of studies considered, it is not possible to rule out a proportion as high as 66%. The authors calculated relative risk across all studies that yielded a relative risk of 1.18 (95% confidence interval: 1.12-1.25). Thus, although the published data support a weak association at best, with considerable unexplained variation among studies, new studies are warranted because such small excess risks could have large implica-

tions for public health with the high prevalence of alcohol consumption (more than 30%).

Because of insufficient time, a quantitative meta-analysis of dose-response relationships was not conducted. Such an assessment would not only provide a summary estimate of risk but could also be used to detect heterogeneity in the risk estimates by selected characteristics of the studies. This additional meta-analytic work would be an important undertaking in trying to understand the results of the literature in a systematic way.

Future research

Gaps in our understanding of the association between breast cancer and alcohol might be filled with the help of the following:

- Studies that assess alcohol intake over a lifetime (which would include detailed measurements of alcohol consumption at different ages as well as the duration of drinking alcohol)
- Studies that clearly define and differentiate between pre- and postmenopausal women and analyze the data for these groups separately, as these subpopulations likely have different etiologies and risk factors, and alcohol may affect them differently
- Detailed information on receptor status (estrogen, progesterone, and possibly others)
- Studies that investigate statistical interactions between alcohol and other risk factors: in particular, investigations of interactions with other molecular biological markers, such as genes that code for the p53, the cytochrome P-450 systems, and others.

— CHAPTER 3 —
Review of Anthropometric Factors and Breast Cancer

Christine Friedenreich, PhD

This literature review explores the association between breast cancer and anthropometric factors (body shape and size). The author reviewed all the epidemiological literature published to September 2000.

The review begins by describing the relevant epidemiological studies on the association between anthropometric factors and breast cancer, then proceeds to discuss the biological mechanisms that are hypothesized regarding this association. After raising concerns about the methodological limitations of the studies, the review concludes with recommendations for future research.

Epidemiological studies

An individual's body shape and size are represented by several measures, some of which are interrelated. This review considers studies that examine the specific associations between breast cancer and height, weight, body mass index (weight/height^2), fat deposition patterns, weight change, and breast size. The main methodological issues are how and when in life these measurements are taken and the timing of the measurements. The impact of anthropometric factors on breast cancer risk is modified by menopausal status, hence, all associations must be considered separately for premenopausal and postmenopausal women.

For premenopausal women, there is an increased breast cancer risk with increasing height, a decreased risk with higher weight or body mass index, and no association with increased central adiposity. For postmenopausal women, an increased risk of breast cancer is found with increasing levels of all the anthropometric variables considered, including height, weight, body mass index, waist-hip ratio, waist circumference, and weight gain. Weight loss appears to decrease risk, particularly if it occurs later in life. Breast size may be a risk factor for breast cancer; however, the current evidence is inconclusive. The evidence of increased risk with increased weight and weight gain after menopause is fairly consistent across studies, and the magnitude of the association is also fairly strong.

Biological mechanisms

Several hypotheses exist to explain the biological mechanisms linking anthropometric factors and breast cancer risk. Obesity may increase levels of circulating endogenous sex hormones, insulin, and insulin-like growth factors, all of which, in turn, increase breast cancer risk. Genetic predisposition to obesity and to specific body fat distributions is also implicated. The obese individual has more fat tissue, which can store toxins and serve as a continuous source of carcinogens.

Future research

Gaps in our understanding of the association between breast cancer and anthropometric factors might be filled with the help of the following:

- New and improved methods for assessing anthropometric factors to ensure standardized, reliable, and validated results
- More complete examination of confounding and effect modification by other risk factors
- Observational epidemiological studies designed to capture anthropometric measures throughout the study subject's lifetime so that the influence of weight change can be examined
- Data analyses that consider the underlying biological mechanisms
- More attention to different population subgroups since these minorities may have different risk associations with these anthropometric factors
- Breast cancer prevention trials of weight-loss interventions and intermediate endpoints for breast cancer, especially given that evidence already exists to suggest weight-control strategies throughout life will reduce postmenopausal breast cancer risk
- Intervention trials of dietary change, physical activity, and weight control that examine the relative contribution of each risk factor for breast cancer risk reduction
- Research that clarifies the operation of numerous biological mechanisms
- Studies that incorporate biological measurements of putative determinants of risk so that the associations between these biomarkers and anthropometric factors can be appropriately investigated
- Research on weight-control interventions, strategies, and policies as the means for the primary prevention of breast cancer.

— CHAPTER 4 —
Review of Physical Activity and Breast Cancer

Christine Friedenreich, PhD

This literature review explores the association between breast cancer and physical activity. The author reviewed all the epidemiological literature published to September 2000.

The review begins by describing the relevant epidemiological studies and proceeds to discuss the biological mechanisms that may explain how physical activity affects breast cancer. After raising concerns about the methodological limitations of the studies, the review concludes with recommendations for future research.

Epidemiological studies

Of the 32 cohort and case-control studies of physical activity and breast cancer reviewed, 21 found an inverse association, 9 observed no effect, and 2 studies noted a possible increased risk among the most physically active women. The magnitude of the decrease in risk ranged from 10% to 70%, the majority of studies observing a 30% to 40% decrease in risk among the highest activity categories. Evidence for a dose-response effect was found in 13 of the 21 studies that examined the trend.

No definitive conclusions can be made regarding the effect of physical activity in specific subgroups of the population, since only a few studies examined these effects and the results obtained across studies were inconsistent. There was some suggestion that total physical activity was the most etiologically relevant parameter to measure in these studies, and that activity that was sustained over a lifetime, as opposed to activity performed only during a specific life period, provided the maximum benefit for reducing breast cancer risk. Furthermore, the exact level of activity associated with breast cancer risk reduction cannot be determined from these studies because they used widely varying definitions of activity and did not consistently measure the frequency, intensity, and duration of activity. Hence, based on these studies, there is some evidence that physical activity reduces breast cancer risk; however, the exact magnitude of the risk reduction is unknown. Furthermore, the type of activity, the level of activity, and the period(s) in life when physical activity exerts the most benefit have not been established.

Biological mechanisms

Three main biological mechanisms have been hypothesized to explain how physical activity may prevent or delay breast carcinogenesis. Physical activity may influence breast cancer risk by decreasing endogenous estrogen exposure, by decreasing obesity and abdominal fat mass, and by improving immune function. Physical activity may also influence risk through correlated risk factors that share the same causal pathway. Since physical activity, dietary intake, and anthropometric factors are interrelated breast cancer risk factors, the individual and joint effects of these factors require further investigation.

Methodological limitations

A number of methodological limitations to the studies were identified, including error in the measurement of

physical activity, inadequate control for confounding, and incomplete examination of effect modification. Errors in the measurement of physical activity could have had the effect of reducing the magnitude of the risk estimates by biasing the results toward the null. Likewise, the true magnitude of the association between physical activity and breast cancer may have been masked by residual confounding and by lack of examination of the effect within subgroups of the study population. Physical activity is likely to influence breast cancer risk differentially within major population subgroups; however, too few studies have examined these subgroups to make any definitive conclusions about such effects.

Future research

Gaps in our understanding of the association between breast cancer and physical activity might be filled with the help of the following:

- Improved methods of measuring that capture all *types* of physical activity (i.e., occupational, household, and recreational), and that measure all *parameters* of activity (i.e., frequency, intensity, and duration) across *entire lifetimes* (i.e., from childhood to the reference year)
- More observational epidemiological studies that use better measurement of physical activity, include all possible confounding factors, and examine the effect of activity within subgroups of the population to assess effect modification completely
- More research on the underlying biological mechanisms in order to clarify the mechanistic pathways through which physical activity influences breast cancer risk and to allow physical activity and cancer prevention intervention studies
- Investigations that would permit the development of more precise prescriptions on the type of activity, the level of activity, and the period in life when physical activity might reduce the risk of breast cancer (intervention studies would be the ultimate objective in future research in physical activity and breast cancer prevention).

— CHAPTER 5 —
The Association Between Breast Cancer and Active Smoking and Exposure to Environmental Tobacco Smoke

Mark Goldberg, PhD, Janet Faith, MSc, Sally Campbell, MSc, Marie France Valois, MSc

This literature review explores the association between breast cancer and active smoking or exposure to environmental tobacco smoke (ETS). The authors reviewed epidemiological studies in English published between 1966 and 1999.

The review begins by describing the studies and proceeds to analyze the results for both active smoking and ETS. (The study results are summarized in tabular form at the end of the original review.)

Epidemiological studies

A total of 50 case-control studies and 12 cohort studies that reported an association between active smoking or ETS and breast cancer (postmenopausal, premenopausal, or premenopausal and postmenopausal combined) were reviewed. In attempting to develop a metric for active tobacco smoking, the authors found that smoking status was the most common index reported in the studies; this index consisted of categories for "never," "former," or "current" smokers. In addition, cumulative tobacco smoking, usually expressed as pack-years, was used.

In the cohort studies, smoking status, as measured at time of entry, was commonly assessed, as was cumulative tobacco smoking and number of cigarettes per day. The authors deemed that a study showed that the risk of breast cancer was elevated if the estimated relative risk for current active smoking status was significantly greater than unity (95% confidence limits excluding unity) or if one of the following conditions was met:

- There was evidence of a monotonic increase in risk by consumption—usually if the test for linear trend was statistically significant (p value < 0.05).
- The 95% confidence limits associated with the odds ratio or relative risk for the categories of highest consumption when compared with the lowest category excluded unity.

For environmental tobacco smoke, no single measure was representative. Because of this and the small number of studies in which ETS was measured, the decision was made not to estimate the proportion of positive studies.

Results

Overall, the proportion of positive studies for active smoking (31%) was well below what one would expect by chance alone. A summary estimate of relative risk was calculated using standard meta-analytic techniques for "never" smokers, "current" smokers, and "former" smokers. Across all studies, very small but statistically significant effects were found for all three metrics of active smoking (pooled relative risks between 1.06 and 1.09). In addition, there were few studies that showed a monotonic increase in risk with increasing exposure,

although it is unlikely that these studies had sufficient power to detect dose-response relationships with very shallow slopes.

On the basis of the small, pooled relative risks and the lack of findings of dose-response relationships, the authors tentatively conclude that the data do not support an association between active smoking and breast cancer. However, the possibility that there are small excess risks cannot be excluded; small excess risks could have implications for public health because the prevalence of smoking is quite high (more than 30%).

There are too few studies of environmental tobacco smoke to make any definitive conclusions. Many studies were small and thus the power to detect very small excess risks was also quite small.

Future research

Gaps in our understanding of the association between breast cancer and exposure to tobacco smoke might be filled with the help of the following:

- Studies that clearly define pre- and postmenopausal women and analyze the data for these groups separately, as these subpopulations likely have different etiologies and risk factors, and tobacco smoke may affect them differently
- Detailed information on receptor status (estrogen, progesterone, and possibly others)
- Detailed biological data to determine whether or not there are any specific gene-environment interactions (e.g., genes that code for the p53 and cytochrome P-450 enzyme systems or acetylization status).

— CHAPTER 6 —
Literature Review of Associations Between Breast Cancer and Occupational Exposures

France Labrèche, PhD

This literature review explores the association between breast cancer and occupational exposure to chemicals, radiation, electromagnetic fields (EMF), and working conditions in a range of industries. The author reviewed the literature published between 1994 and September 2000.

The review begins by describing the possible biological mechanisms linking occupational exposures to breast cancer in three categories: chemical exposures, physical exposures, and organizational exposures. The review then proceeds to classify studies reviewed as either descriptive or analytical, and to describe the results according to the industry or the occupation or the nature of the exposure. The review concludes by making recommendations for future research.

Biological mechanisms

Several hypotheses can be referred to when considering biological mechanisms that may link occupational exposures and breast cancer. The majority of exposures can be classified as exerting direct and indirect effects on breast cancer, regardless of their chemical, physical, or organizational nature.

Chemical exposures

One hypothesis proposes that certain types of chemicals, namely organic solvents, are concentrated in the non-lactating breast and stagnate in the milk ducts, where they are then transformed into reactive metabolites that exert detrimental effects.

Because breast cancer is an estrogen-related cancer, it is also plausible that chemicals mimicking an estrogen could act on breast cancer risk: this hypothesis is favoured with regard to organochlorines and other halogenated chemicals. Interference with the immune function or induction of cytochrome P-450 could be additional pathways of action.

Physical exposures

Exposure to physical agents has also been linked to breast cancer through direct and indirect effects. For instance, exposure to ionizing radiation has been proven to cause different types of cancer in humans, probably through a mechanism involving direct DNA damage.

An example of an indirect action would be that of electromagnetic fields (EMF) exposure: the energy conveyed by these fields appears insufficient to cause direct cell damage, but does appear sufficient to reduce the normal production of melatonin, an immunostimulatory regulating hormone. Stevens and colleagues hypothesize that breast cancer risk is increased by exposure to EMF because EMF interferes with the oncostatic properties of melatonin and allows levels of estrogen and prolactin to increase, thus indirectly affecting hormonal secretions.

Organizational exposures

An organizational factor that may be associated with breast cancer is "light-at-night"—the exposure to light that occurs when individuals work rotating shifts or full night shifts. This exposure is known to lead to a rapid decrease in the production of melatonin.

Another organizational factor is the amount of physical activity required by a given job. Several hypotheses have been proposed regarding the relationship between physical activity and breast cancer. These include the beneficial effect of physical activity on immune function, anti-estrogenic effects (among both pre- and postmenopausal women), and the reduction of obesity, which reduces the amount of body fat available for the storage of harmful chemicals.

Results

Studies considered in this review were classified as either descriptive studies (considered as indicators of possible associations) or analytical studies (case-control and cohort studies), the latter being given more weight.

Chemical and pharmaceutical industries

Results from studies of occupations in the chemical and the pharmaceutical industries and from studies of particular chemical substances are not consistent. Moreover, workers in these industries are exposed at various levels to a wide array of chemicals, thus complicating the interpretation of the results. It should also be noted that many of the published studies were done by the chemical or pharmaceutical companies themselves.

Clerical and professional sectors

Numerous descriptive studies based on administrative data have reported associations of female breast cancer (incidence or mortality) with clerical and professional jobs (other than health care occupations). For a few occupational categories, the number reporting statistically significant excess risks was rather impressive. The fact that exposures to specific occupational agents cannot be identified easily in most of these occupational groups makes interpretation of the results difficult. The excess risks reported for these occupations may very well have been confounded by reproductive factors. In addition, there are no estimates of risk by duration of employment.

Cosmetic, hair, and beauty industries

According to the available literature, there is little evidence that cosmetologists, hairdressers, and beauticians have an increased risk of breast cancer. However, a few recent positive studies present elevated risk estimates, and given that some cosmetic and hair products contain substances that have been classified as possibly or probably carcinogenic (e.g., dichloromethane, perchloroethylene, formaldehyde, some pigments, amines), this economic sector deserves further study.

Airline industry

Flight personnel are exposed to cosmic radiation, EMF, ultraviolet radiation, pesticides, and jet fuel emanations. Very few studies have been done on these workers, and so far the risks identified are at a level that could be attributable to confounding factors.

Agricultural/horticultural industry

It appears that being a farmer, a gardener, or a worker who must handle pesticides does not entail an increased risk of developing or dying from breast cancer, even though these occupations involve exposure to chemicals that have been linked to some types of cancer.

Health care sector

The health care sector is extremely varied in terms of kinds of occupations and types and levels of exposures. Studies of nurses and nurse assistants do not provide strong evidence of an association with breast cancer. However, there is evidence that working in a routine or research laboratory could possibly be associated with an increased risk.

Manufacturing industries

None of the available studies of rubber and plastic product makers, and of wood and pulp and paper industries showed increased risks, but, unfortunately, most of them investigated mortality only, and almost all of them had very little power to detect an increase in risk.

Ionizing radiation

Although exposure to ionizing radiation is a recognized risk factor for breast cancer, so far none of the studies has shown convincing excess risks. This lack of association is probably due to a number of factors: the low cumulative radiation doses experienced by x-ray technicians and atomic energy workers, the imprecision of measurements in most studies, the somewhat short follow-up, and other confounders and biases.

Electromagnetic fields (EMF)

Few epidemiological studies have been carried out among female workers exposed to EMF. Although there are many inconsistencies in the exposure measurements, the more

recent studies that take menopausal status into account and look at incidence instead of mortality start to converge toward showing an association between EMF exposure and breast cancer for premenopausal women.

Organochlorines and organic solvents

The popularized hypothesis linking breast cancer to organochlorine exposure deals with dietary and environmental exposures rather than occupational exposure. The existing occupational studies are inconclusive concerning this possible link, as they are regarding the evidence of an association between organic solvents as a group and breast cancer. Again, most studies looked at mortality and very few took menopausal status into account.

Occupational physical activity

The available literature on occupational physical activity suggests that it could possibly decrease breast cancer risk, but there are still some discrepancies between studies.

From the available literature, we can infer that workers in the following occupations may be exposed to increased risk of breast cancer:

- occupations entailing EMF exposure
- occupations entailing exposure to mixtures of chemicals, including solvents (e.g., laboratory workers, especially in the biomedical fields)

Because few high-quality studies directed specifically at assessing occupational breast cancer risks have been carried out, it is not possible to unambiguously identify occupational risk factors for breast cancer.

Future research

Gaps in our understanding of the association between breast cancer and occupational exposures might be filled with the help of the following:

- Use of refined indicators of occupational exposures (especially for "new" exposures such as EMF)
- Development of biological markers of exposure in the case of fugitive exposures to very reactive compounds
- Better analyses of exposure-response trends that take into account error factors inherent in retrospective exposure assessments
- Studies that focus on incidence data and rely as much as possible on histologically confirmed cases
- Studies that consider the estrogen- and progesterone-receptor status of the tumors, and always take into account menopausal status
- Exploration of substances or circumstances that may disrupt hormonal balance.

— CHAPTER 7 —
The Association Between Breast Cancer and Exposure to Extremely Low Frequency Electromagnetic Fields

Mark Goldberg, PhD, Maria-Graciela Hollm, BSc

This literature review explores the association between breast cancer and exposure to electromagnetic fields. The authors reviewed epidemiological studies in English, French, and Spanish published between 1966 and 1999.

The review begins by describing the studies and proceeds to analyze the results and make recommendations for future research. (The study results are summarized in tabular form at the end of the original review.)

Epidemiological studies

During the past 20 years, there has been enormous interest in the possible relationship between electromagnetic fields (EMF) and breast cancer. In 1998, the U.S. National Institutes of Health called for greater research on EMF, declaring it a potential human carcinogen, and the International Agency for Research on Cancer stated that there is an urgent need for research on EMF and specific types of human cancers.

A total of 30 articles were identified and subdivided according to whether the studies were used to investigate exposure to EMF from occupational sources, residential sources (power lines or appliances), or multiple sources.

Results

The data from these few studies do not provide any persuasive evidence that breast cancer is positively associated with exposure to EMF. One possible explanation of these findings is that EMF does not cause breast cancer. The data are not, however, particularly strong, as there are limitations with many of the epidemiological studies, particularly the occupational ones, that would lead to attenuated estimates of risk and reduced statistical power to detect small effects, should they exist.

Limitations of these studies include exposure misclassification, misclassification of disease status (especially for the death certificate studies), and lack of control for essential confounding variables. The issues about misclassification and power are particularly relevant, as it is likely that the magnitude of the association will not be large. Most of these studies could not detect excess risks in the order of 20% to 50%.

Future research

Gaps in our understanding of the association between breast cancer and exposure to electromagnetic fields might be filled with the help of the following:

- Studies that measure all relevant confounding factors and have sufficient statistical power to detect small excess risks
- Studies that take into account menopausal status and estrogen-receptor status
- Use of more accurate sources of information on exposure.

— CHAPTER 8 —
Organochlorines: A Meta-analysis

Christy G. Woolcott, MSc, Kristan J. Aronson, PhD

This literature review explores the association between breast cancer and organochlorines, a large class of lipophilic, chlorine-containing organic chemicals that includes dioxins, furans, DDT and its metabolite DDE, and polychlorinated biphenyls (PCBs). The authors reviewed the epidemiological literature published to November 2000.

The review summarizes the results of studies that have explored the carcinogenicity of different organochlorines, and concludes with recommendations for future research.

Epidemiological studies

Thirty-three research articles presenting data from 26 studies examining breast cancer risk in relation to exposure to a variety of organochlorines were reviewed.

Organochlorines are the focus of research, in part, because they were used widely in the past and have become ubiquitous in the environment as a result of a complex chemical structure that makes them resistant to degradation. The primary exposure route for humans is through food. Organochlorines are now found in the adipose tissue of almost all humans and could plausibly affect breast cancer risk by acting as direct carcinogens or by acting as agonists or antagonists of steroid hormones, such as estrogen and androgens.

Results

In general, the results from the studies of the association between total PCBs and breast cancer risk are null; the summary odds ratio from all the studies combined was 0.94. The results from the studies were noticeably heterogeneous, but none of the design characteristics investigated significantly helped to predict variation among studies. Results from studies reporting congener-specific analyses were inconsistent and not convincing. Only a few of the investigators have done analyses examining the effect of the correlations among PCB congeners.

The results from the studies of the association between DDE and breast cancer risk are also close to the null. The estimation of an odds ratio for the increase in 1000 nanograms DDE per gram lipid was 1.03. Exclusion of individual studies would not change the observation that the summary odds ratio is very close to the null. None of the design characteristics investigated significantly helped to predict variation among studies. The results of investigations of other organochlorines (mostly pesticides) have not revealed convincing associations either.

Future research

Gaps in our understanding of the association between breast cancer and exposure to organochlorines might be filled with the help of the following:

- Exposure assessment that measures exposure within critical time periods for breast cancer carcinogenesis rather than cumulative exposure
- Development and use of methods that examine the impact of different mixtures of organochlorines: for instance, researchers could investigate

individual contaminants while controlling for others, summing the levels of contaminants in different structure-activity groups (e.g., estrogenic, androgenic, dioxin-like)
- Use of statistical techniques such as principal-components analysis to estimate the joint effects of congeners
- Use of a total toxic-equivalency approach to assess exposure to dioxin-like effects or total estrogen equivalency
- Studies of effect modifiers that influence the metabolism of organochlorines or that work in the same pathway of carcinogenesis as organochlorines: candidates for this research include polymorphisms in genes encoding cytochrome P-450 enzymes, aromatase, catechol-O-methyltransferase, estrogen receptors, and the androgen receptor
- Studies of other factors that affect the concentration of organochlorines in the body, such as body mass index, parity, and lactation history
- Studies of organochlorines and contaminants with endocrine-disrupting effects, such as tris(4-chlorophenyl)methane, tris(4-chlorophenyl)methanol, and alkylphenol ethoxylate surfactants.

— CHAPTER 9 —
Emerging Hypotheses and Methodological Approaches in Breast Cancer Etiology

Kristan J. Aronson, PhD, Christy G. Woolcott, MSc

This literature review explores emerging hypotheses and methodological approaches in breast cancer etiology. The authors reviewed the epidemiological literature published to February 15, 2001.

The review discusses risk factors that might be worth investigating: pharmaceuticals, environmental and industrial substances, viruses, hormones, growth factors and receptors, and early life events. The review also discusses biological pathways that might be studied, and methods and techniques that might be incorporated into epidemiological studies of risk factors. The review concludes with recommendations for future research.

Epidemiological studies

Literature reviews and interviews with key informants led to the identification of specific biological pathways, risk factors, and methodological approaches that might be used to further our understanding of breast cancer etiology. Scientific evidence for the new potential risk factors considered here is weak by definition, simply because too few studies have been conducted to date.

Results

In the process of reviewing current literature, the authors found that few specific factors can be labeled as "new" or "emerging." Some factors worthy of this designation are covered in other parts of *Review of Lifestyle and Environmental Risk Factors for Breast Cancer* (e.g., phytoestrogens and vitamins are mentioned in Chapter 1, and organochlorines are considered in Chapter 8).

During the literature review the authors also found that future etiological research might be advanced through an awareness of biological pathways and the use of specific methodological approaches. While these methodological approaches may not, strictly speaking, involve emerging hypotheses, incorporating them into epidemiological studies of risk factors may lead to an improved understanding of the etiology of breast cancer.

Biological pathways

Numerous biological mechanisms are invoked as the rationale for epidemiological studies. These include interference with the endocrine system, induction of genetic lesions, and alteration of mitotic processes, to name just a few. Programmed cell death or apoptosis is known to be a key process in tumour growth. It would be of interest to learn whether modifiable factors that are found to affect apoptotic pathways in the laboratory setting also affect breast cancer in human population studies. The fetal antigen hypothesis, which has been put forth to explain the seemingly paradoxical finding that breast cancer risk increases in women for a short time following a pregnancy but then falls below that of nulliparous women, is also worth further study. More research is

needed to confirm to what extent these proposed mechanisms are active in causing breast cancer.

Emerging risk factors

Environmental and industrial substances

Ubiquitous environmental chemicals that may be "endocrine disrupters" have been the focus of some recent breast cancer research (see Chapter 8, discussion of organochlorines). Some chemicals, even those labeled as endocrine disrupters, may actually contribute to cancer development through other mechanisms (e.g., through direct DNA damage). Chemicals able to disrupt endocrine system function include plasticizers such as phthalates, alkylphenols and bisphenol A, and other "endocrine-active" fungicides, pesticides, and herbicides. Organohalogens, another class of endocrine-disrupting chemicals, are being investigated and particular attention is being paid to polybrominated biphenyl ethers (PBBEs), which are used as flame retardants.

Finally, a few other factors mentioned in this section are heavy metals, especially cadmium, the water disinfection byproduct MX, styrene, and air pollution.

Pharmaceuticals

Very few epidemiological studies have been conducted to assess the possible association between breast cancer and exposure to pharmaceuticals. A few surveillance and case-control studies have been published, and more investigation is required.

Viruses

Investigating the etiologic role of viruses has regained popularity recently. A recent article presenting a descriptive study and a large analytic study in the U.S. provides some support for the hypothesis that delayed primary Epstein-Barr virus (EBV) infection may contribute to increased breast cancer risk

Social factors

Social factors that may act as possible upstream events in the causal chain of breast carcinogenesis should be investigated, now that techniques of social epidemiology are becoming more precise and relevant variables are being identified.

Hormones

Investigating endogenous hormones as risk factors for breast cancer is not new, but new hypotheses and methodologies have emerged recently. These, along with recent expert meetings and published reviews, have stimulated new interest in a potentially important area. For example, a new hypothesis suggests that estradiol can play a dual role in carcinogenesis, inducing genetic lesions and stimulating hormone receptor-mediated proliferation.

Growth factors and receptors

Our understanding of the associations between hormones, growth factors and receptors, and the risk of breast cancer might be improved by broadening the array of hormones investigated beyond estrogens and estrogen receptors. For example, since the interaction between the epithelial cells and stroma is important in carcinogenesis, factors such as insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3), which affect the development of the stromal components, could be examined.

Early life events

The idea that exposure to carcinogens when the breast is in a state of low differentiation may lead to breast cancer suggests that investigation of the in utero environment might be worthwhile. Further investigation of the impact of being breastfed on the individual's risk of breast cancer might also be useful.

Methodological approaches

Renewed emphasis on methodological approaches could improve investigations of breast cancer etiology and risk factors. A greater emphasis on creative interpretation of surveillance data, animal research, and analogies made with other diseases and risk factors might help generate promising hypotheses. Methods that permit more precise timing of exposure should be developed. Exposures need to be determined over the individual's lifetime relative to developmental events (i.e., pre- and perinatal period, menarche, first full-term pregnancy, menopause). Innovative methods of determining exposure during early life stages should also be developed. Biological markers are needed to provide more precise measurement of internal doses when studying exposure. As well, more research into disease subgroups should now be possible with the increasing use of molecular techniques in pathology, and more research into genetic influences should be possible with the recent publication of the human genome. Finally, more consideration should be given to the study of intermediate endpoints for breast cancer, such as mammographic density.

Future research

Gaps in our understanding of breast cancer etiology might be filled with the help of the following:

- Studies that explore the mechanistic pathways of breast carcinogenesis, including apoptosis and factors that affect it, and the fetal antigen hypothesis
- Studies that investigate environmental and industrial substances, including plasticizers, organohalogens, heavy metals such as cadmium, PAHs, biocides, nitrosamines, chlorinated paraffins, the water disinfection byproduct MX, and styrene
- Studies that investigate exposure to pharmaceuticals, including SSRIs and tricyclic drugs
- Studies that investigate viruses, especially Epstein-Barr and mouse mammary tumor virus
- Studies that investigate group or social level determinants of breast cancer risk that may be more amenable to public health interventions
- Studies that investigate hormones, insulin-like growth factors, and subtypes and variants of receptors and binding proteins
- Methodological approaches that emphasize creative interpretation of surveillance data, animal research, and analogies made with other diseases and risk factors in generating hypotheses
- Methods that time exposures over the individual's lifetime relative to developmental events
- Development of methods that measure exposure in early life stages
- Use of biomarkers to measure exposure more precisely
- Development of methods that measure genetic mutations and polymorphisms and permit the investigation of gene-environment interactions
- More examination of interactions between pairs of susceptibility factors and carcinogens that are biologically related
- Use of DNA microarray data to classify diseases by type
- Use of intermediate endpoints for breast cancer such as mammographic density.

— CHAPTER 10 —
Review of the Mechanism of Action of Some Etiologic Risk Factors for Breast Cancer

Rosemonde Mandeville, MD, PhD

This literature review explores the biological mechanisms of four etiologic risk factors for breast cancer: electromagnetic fields, alcohol, polycyclic aromatic hydrocarbons, and organochlorines. The author reviewed relevant articles published to August 2000.

The review begins with a description of the multi-step carcinogenesis model and proceeds to discuss the mechanisms of action for each risk factor. (The original review concludes with a glossary of terms.)

The multi-step carcinogenesis model

Cancer is recognized as a highly complex, multifactorial disease that is caused, in part, by endogenous metabolic or other imbalances associated with age or genetic makeup and, in part, by a wide variety of exogenous factors including diet, lifestyle, and exposure to ionizing radiation and chemicals of natural or synthetic origin. Cancer is also considered to be the end result of a multi-step process in which a large number of endogenous and exogenous factors interact, simultaneously or in sequence, to disrupt normal cell growth and division.

In the design of new approaches to cancer prevention, it is important to realize that most cancers develop stepwise over a long period of time with non-malignant precancerous lesions that only slowly evolve toward cancer. When the effect is considered of many chemicals and some radiation, as well as some viruses (DNA and RNA retroviruses), cancer development can be divided into three major stages or periods: initiation, promotion, and progression.

- *Initiation: Conversion of some normal cells to precancerous cells.* This stage begins with rapid, irreversible change, believed to involve the genetic material of a rare target cell (i.e., changes in 6 or more specific genes out of the 100 000 genes in a cell). Initiation occurs when a chemical or other genotoxic agent damages the DNA of the cell and leads to changes in the base composition in DNA or to gene rearrangements. Initiation can also result from random errors in DNA replication, the mutagenic effect of a chemical (or its metabolite) on DNA, or indirectly from chronic cytotoxicity (resulting in cell turnover and natural errors in cell replication), the activation of cellular oncogenes, or other mechanisms. Initiation can be modulated by factors that change the efficiency of DNA repair or immune surveillance. In the case of chemicals that require metabolic activation, initiation can be affected by factors that modify metabolism.

- *Promotion: Conversion of precancerous cell to cancer cell.* This stage involves the progression and proliferation of the "transformed" cell through a variety of pathological states (e.g., hyperplasia, neoplasia) leading eventually to a malignant tumor. Promotion is characterized by alteration in the genetic expression and growth from initiated cells. From this promotion

phase, histologically recognizable pre-neoplastic lesions emerge. Most do not develop, but some (one is enough) may experience additional genetic changes and give rise to a cell population that is no longer susceptible to cell population size controls. This autonomous growth is a tumor. More changes need to occur if the tumor is to become a spreading type (metastatic).

- *Progression: Development of tumors.* This is a self-generating stage, but it can be modulated by diet or by other drugs and xenobiotics. Progression is characterized by changes in the number and/or rearrangement of chromosomes and leads to increased growth rate, invasion of healthy tissue, and metastasis.

Initiation and promotion each consist of several stages and may involve distinct mechanisms; some of these changes are reversible and some are not, but probably all are susceptible to a variety of modulating factors through which they may be enhanced or inhibited. Also, carcinogenic agents that can induce genetic change are not necessarily the same throughout the neoplastic process and may not act directly on a cell's genetic material. For instance, dioxin does not change DNA directly, but it is still a potent carcinogen. Some agents appear to act through a receptor mechanism. Even if a carcinogen does not directly damage a cell's DNA, changes in gene expression *always* occur during carcinogenesis.

Biological mechanisms

When human cells are exposed to chemical and physical carcinogens they undergo DNA changes (mutations) and changes in gene expression. A number of molecular and cellular mechanisms may be operative with the four different agents under discussion here.

Electromagnetic fields (EMF)

In the 160 studies reviewed, it is generally accepted that extremely low frequency (ELF) electromagnetic fields (EMF) do not transfer energy to cells in sufficient amounts to directly damage DNA. However, it is possible that certain cellular processes altered by exposure to ELF-EMF (such as processes involving free radicals) may indirectly affect the structure of DNA. Most investigators have looked for strand breaks and other chromosomal aberrations, including sister chromatid exchange, formation of micronuclei, and/or effects on DNA repair.

The body of evidence on signal transduction suggests that magnetic fields < 100 µT and electric fields < 1 mV/m are likely to have some effect on a number of signal transduction–related pathways in mammalian cells. Most of the studies, even those that appear to have been performed carefully, were reported from single laboratories, and the results cannot be considered conclusive. Blocking of antiproliferative effects has been replicated at 1.2 µT, but the physiological significance is unknown.

Preliminary studies in transformed breast cancer cells suggest that ELF-EMF exposures can overcome effects of melatonin and tamoxifen in regulating cell growth. This effect of ELF-EMF appears to occur at magnetic field exposures that may be encountered in the environment. Several other laboratories have presented similar, unpublished findings at national meetings. The importance of this finding for human health is unclear, but considering the magnitude of the incidence of breast cancer, this area warrants further investigation.

Alcohol

Several possible mechanisms have been proposed to explain the potential etiologic role of alcohol in breast cancer. However, these mechanisms are not supported by sufficient evidence, nor do they explain well the features of the association.

Wright and colleagues have proposed an explicit model for alcohol-induced Reactive Oxygen Species (ROS = partial reduction products of oxygen) that depends on the combined activities of metabolic enzymes. Moreover, the direct action of cytochrome P-450 2E1 on ethanol in the mammary gland may be an additional source of carcinogenic ROS. Although the role of ROS in carcinogenesis is still being defined, the amelioration of several cancers, including breast cancer, by antioxidants underscores the importance of confirming this mechanism. Alcohol-derived ROS could contribute to several stages in breast cancer development. For example, alcohol-derived ROS could act at an early stage of mutagenesis leading to tumor initiation and breast cancer, at later stages of progression and transformation to a cancer phenotype, or could perhaps affect cell proliferation.

Polycyclic aromatic hydrocarbons (PAHs)

Benz(a)pyrene, dibenz(a)anthracene, and 1-nitropyrene are examples of known experimental breast carcinogens that induce and promote altered DNA by increased intracellular pro-oxidant production as well as by direct adduction to DNA. The breast is embedded in a major fat depot, which stores and concentrates polycyclic aromatic hydrocarbons and can metabolize these to carcinogenic metabolites. Ductal cells concentrate these metabolites and themselves become target cells for carcinogenesis.

Organochlorines

PCBs, dioxins, and certain pesticides are examples of organochlorine compounds whose high lipophilicity and stability have contributed to their persistence as environmental pollutants. This persistence has resulted in significant contamination of human food long after the organochlorines were used. Exposure to these compounds prenatally or in early postnatal life can disturb the development of the endocrine system and organs that respond to hormonal signals, and therefore they are termed "environmental endocrine disrupters." During periods of high growth and during breast development, the sensitivity of breast cells to estrogenic compounds is sufficiently great for xenoestrogens to significantly enhance risk for breast cancer. Women exposed early in life to these compounds may have an increased risk for diseases and disorders with a hormonal component, which could include not only breast carcinoma but also other carcinomas of the reproductive system, as well as endometriosis and impaired fertility.

Future research

Gaps in our understanding of biological mechanisms for breast cancer might be filled with the help of the following:

- Studies that investigate the molecular and cellular mechanisms that may be operative when individuals are exposed to EMF, PAHs, and organochlorines
- Studies that investigate the role of alcohol-derived ROS and anti-oxidants in breast cancer development
- Studies on the effect of organochlorine exposure early in life
- Studies that investigate gene-environment interactions
- Studies that use DNA microarray data to identify proteins implicated in the carcinogenesis of breast cancers
- Studies aimed at the development of novel biological markers of exposure (e.g., polymorphism in genes encoding cytochrome P-450 enzymes, catechol-o-methyltransferase)
- Studies that investigate the effect of EMF on hormonal status and genes regulating estrogens and androgens.

— CHAPTER 11 —
Breast Cancer Etiology and Prevention from an Evolutionary Perspective

Katherine E. Wynne-Edwards, PhD

This literature review explores the evolutionary biology of the breast and the association between breast cancer etiology and lifestyle changes over the past 10 000 years. The author reviewed literature published between 1966 and October 2000.

The review begins by providing antecedents for the evolutionary perspective and proceeds to discuss various risk factors in terms of this perspective, including endogenous estrogens, diet, nulliparity, late breast feeding, vulnerability of breast tissue to carcinogens, and postreproductive problems. The review then discusses the emergence of breast cancer as a consequence of evolution and concludes with recommendations for future research.

The evolutionary perspective

The evolutionary perspective that guided this review is based on the work of Charles Darwin and some recent researchers. A specific review on the subject is provided because the concepts of Darwinian evolution and their value for predicting disease etiology are largely unappreciated by medical and epidemiological professionals.

Evolutionary biology provides a paradigm in which it is both plausible and consistent to see the relationship between the way breast cancer cell lines emerge as clinical cancer, the inherent role of chance in breast cancer incidence, and the known lifestyle risks associated with modern western civilization. Evolutionary biology also clearly predicts which avenues of prevention and treatment research will work with our biology and which will work against Darwinian principles. Thus the evolutionary perspective is both integrative and prescriptive.

Lifestyle risks

Relative to the genes of our hunter-gatherer ancestors, our genes are unchanged, yet modern North American women have an increased, and increasing, incidence of breast cancer. An evolutionary perspective suggests that the majority of known lifestyle risks for breast cancer are the result of recent cultural and reproductive changes in women's lives. These changes have combined to

- increase our exposure to endogenous estrogen, which is a weak carcinogen, by way of early menarche, low parity, abbreviated breast feeding, and pharmaceutical hormone manipulation
- increase the proportion of our lives spent at stages in the developmental biology of breast tissue with a high rate of mitotic cell divisions (cells in breast tissue that has never differentiated to produce milk divide 20 times more often than cells that have acquired the terminal phenotype)

The emergence of breast cancer

Evolutionary biology suggests that our own biology was and is the greatest risk factor in breast cancer incidence.

- Errors in DNA replication always occur. In fact, random mutations (copying errors as well as mechanical and chemical damage) are the essential cause of genetic variation.
- The presence of estrogen (and/or other carcinogens) will increase the frequency of mutations in individuals over their lifetimes. Thus, increasing numbers of mutation errors will accumulate with increasing age, and breast cancer incidence will increase with age.
- Increasing numbers of cell divisions will proportionately increase the risk of mutation in that tissue. Thus, breast tissue that has never produced milk has a high mitotic rate that will randomly accumulate mutations leading to breast cancer.
- Estrogen is a potent mitogenic differentiation signal that breast tissue responds to.

In modern western civilizations we have a high nutritional plane that keeps the ovary active, a low fertility rate achieved through effective contraception, and an older and older population of women postponing or avoiding child-bearing. A percentage of breast cancer cases are undoubtedly due to environmental insults from synthetic carcinogens. However, the majority of cases might be due to "natural" causes—not desirable, but natural.

A single causality for breast cancer will never be found. In a very real sense, each breast cancer is unique and each breast cancer involves bad luck as an essential ingredient. A vast number of environmental and endogenous factors modulate that risk, but it is always going to be a risk. Primary prevention of breast cancer must involve working with a clear understanding of the rules governing the emergence of breast cancer.

Hypotheses based on evolutionary biology are amenable to empirical test and validation. If these evolutionary hypotheses are validated, endogenous risk factors predicted by evolutionary biology might ultimately provide the best explanation for breast cancer incidence. An evolutionary perspective will suggest avenues for research and intervention that will work with our biology to reduce breast cancer incidence.

Future research

Gaps in our understanding of the association between evolutionary biology and breast cancer etiology might be filled with the help of the following:

- Meta-analytic studies that use the best mathematical estimates of risk to analyze existing epidemiological data from an evolutionary perspective: known etiological risks must be reconsidered based on mutation rate and number of cell divisions in the breast while incorporating the changes in menarche, age at first full-term pregnancy, and so on
- Basic research on normal and induced mammary tissue differentiation: many lifestyle risks for breast cancer that we have considered non-modifiable may need to be modified. (Although we cannot suggest that modern North American women bear their children in their teens, we may consider providing an endocrine signal to their breast tissue that differentiates those cells into the terminal phenotype and thereby lowers lifetime cell divisions and risk.)
- Interdisciplinary collaborations: specialists in evolutionary biology, species divergence, and natural selection in populations of unicellular organisms might work with cancer researchers to apply their models and perspectives to predicting the emergence of clinical breast cancer and the responses of cancer and precancerous cells.

Conclusion and Recommendations for Future Research

Kristan Aronson, PhD, Christine Friedenreich, PhD, Mark Goldberg, PhD

The literature reviews prepared by the Working Group on Primary Prevention of Breast Cancer reveal many gaps in our understanding of breast cancer etiology. The research needed to fill these gaps can be considered in terms of substantive and methodological issues.

Substantive issues

The authors of *Review of Lifestyle and Environmental Risk Factors for Breast Cancer* found that further research is warranted, in some capacity, in all of the areas they reviewed:

- Diet
- Alcohol consumption
- Anthropometric factors
- Physical activity
- Active smoking and exposure to environmental tobacco smoke
- Occupational exposures
- Electromagnetic field exposure
- Organochlorines
- Emerging hypotheses and methodological approaches
- Biological mechanisms for breast cancer
- Evolutionary etiology of breast cancer

More studies of all kinds—biological, meta-analytic, and observational epidemiological—are needed. Intervention trials are also needed, especially in the areas of diet, weight-control, and physical activity.

The fact that 65% to 70% of newly diagnosed breast cancer cases are associated with no established risk factor other than age suggests that much more etiologic research is necessary. The Working Group recommends that researchers consider undertaking research in the following areas:

- *Studies that explore the underlying biological mechanisms of breast cancer in order to clarify the mechanistic pathways through which various factors influence breast cancer risk.* This kind of clarification would make cancer prevention intervention studies feasible and help answer questions about the possible beneficial effect of certain nutrients and kinds of physical activity.
- *Research that explores specific gene-environment interactions.* The study of genes that code for the p53 and cytochrome P-450 enzyme systems would be helpful when investigating the roles of alcohol, tobacco smoke, and environmental chemicals in breast cancer development.
- *Studies that take menopausal status and estrogen- or progesterone-receptor status into account.*
- *Studies that pay attention to different population subgroups.* These studies are needed because subgroups likely have different etiologies and risk associations, especially in terms of anthropometric factors.

- *Research that explores substances or circumstances that may disrupt hormonal balance and thus lead to breast cancer*. This research would be especially useful in the areas of environmental, occupational, and electromagnetic exposures.
- *Research that provides insights into the biology of the breast*. Work in the area of normal and induced mammary tissue differentiation might permit the development of an endocrine signal to lower lifetime cell divisions and breast cancer risk.
- *More multidisciplinary collaborations*. Studies that combine the expertise of specialists in epidemiology, molecular biology, evolutionary biology, chemistry, and pathology could improve the potential for research to discover the causes of breast cancer. Emphasis must be on multidisciplinary projects that test or generate hypotheses regarding the etiology of breast cancer. Such projects have the potential to elucidate biological mechanisms, to identify subgroups of women at higher than average risk of developing breast cancer, and to reduce the incidence of breast cancer.

Methodological issues

The Working Group suggests that improvements in research methodology are needed. In particular, studies that are designed to collect more accurate information about exposures and that have more power to detect small increases in relative risk are needed to clarify the association between specific risk factors and breast cancer. Where an exposure is prevalent, small increases in relative risk could translate into a large number of preventable breast cancer cases. The Working Group recommends that researchers consider the following improvements in methodology:

- *More precise and comprehensive methods of assessment that accurately determine exposure to risk factors*. For example, data on alcohol consumption need to be collected at different ages, while data on physical activity need to be collected for all types of physical activity (i.e., occupational, household, and recreational) and across entire lifetimes (i.e., from childhood to the reference year). Many studies could benefit from the collection of data regarding early life exposure and exposure relative to certain developmental events.
- *Analyses of exposure-response trends that account for errors inherent in retrospective exposure assessments*. In fact, all studies could benefit from the use of statistical methods that address measurement errors. Future research studies also need more complete examination of confounding and effect modification by other factors.
- *Expanded and refined use of biological markers*. In the case of occupational exposure, biological markers could be used to identify fugitive exposure to very reactive compounds. In addition, continued development and use of disease markers should be encouraged to address the potential heterogeneity in risk within subtypes of breast cancer.

Undoubtedly, the kind of research needed to explain how various factors influence breast cancer risk is labour-intensive, time-consuming, and challenging to conduct. But given the continuing increase in breast cancer incidence and the burden the disease places on individuals, families, the health care system, and society, research that ultimately leads to the development of prevention strategies is extremely valuable.

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— APPENDIX —
Recommendations (by topic)

Diet

Gaps in our understanding of the association between breast cancer and diet might be filled with the help of the following:

- Improved dietary assessment methods
- Statistical methods that address measurement errors
- Observational and intervention studies that use more biological markers of long-term dietary exposure
- Observational epidemiological studies that concentrate on measuring early life exposures and dietary patterns
- Observational epidemiological studies that (1) include ethnic and racial minorities, (2) examine effect modification and control for confounding, and (3) investigate more nutrient subtypes (e.g., dietary fatty acids)
- Intervention trials of specific dietary changes and intermediate and long-term endpoints
- More research on the underlying biological mechanisms that may be operative

Alcohol consumption

Gaps in our understanding of the association between breast cancer and alcohol consumption might be filled with the help of the following:

- Studies that assess alcohol intake over a lifetime and include detailed measurements of alcohol consumption at different ages as well as the duration of alcohol consumption
- Studies that clearly define and differentiate between pre- and postmenopausal women and analyze the data for these groups separately, as these subpopulations likely have different etiologies and risk factors, and alcohol may affect them differently
- Detailed information on receptor status (estrogen, progesterone, and possibly others)
- Studies that investigate statistical interactions between alcohol and other risk factors: in particular, investigations of interactions with other molecular biological markers, such as genes that code for the p53, the cytochrome P-450 systems, and others

Anthropometric factors

Gaps in our understanding of the association between breast cancer and anthropometric factors might be filled with the help of the following:

- New and improved methods for assessing anthropometric factors to ensure standardized, reliable, and validated results
- Observational epidemiological studies designed to capture anthropometric measures throughout the study subject's lifetime so that the influence of weight change can be examined
- More complete examination of confounding and effect modification by other risk factors
- Data analyses that consider the underlying biological mechanisms
- More attention to different population subgroups since these minorities may have different risk associations with these anthropometric factors

- Breast cancer prevention trials of weight-loss interventions and intermediate endpoints for breast cancer, especially given that evidence already exists to suggest weight-control strategies throughout life will reduce postmenopausal breast cancer risk
- Intervention trials of dietary change, physical activity, and weight control that examine the relative contribution of each risk factor for breast cancer risk reduction
- Research that clarifies the operation of numerous biological mechanisms
- Studies that incorporate biological measurements of putative determinants of risk so that the associations between these biomarkers and anthropometric factors can be appropriately investigated
- Research on weight-control interventions, strategies, and policies as the means for the primary prevention of breast cancer

Physical activity

Gaps in our understanding of the association between breast cancer and physical activity might be filled with the help of the following:

- Improved methods of measuring that capture all *types* of physical activity (i.e., occupational, household, and recreational), and that measure all *parameters* of activity (i.e., frequency, intensity, and duration) across *entire lifetimes* (i.e., from childhood to the reference year)
- More observational epidemiological studies that use better measurement of physical activity, that include all possible confounding factors, and that examine the effect of activity within subgroups of the population to assess effect modification completely
- More research on the underlying biological mechanisms in order to clarify the mechanistic pathways through which physical activity influences breast cancer risk and to allow physical activity and cancer prevention intervention studies
- Investigations that would permit the development of more precise prescriptions on the type of activity, the level of activity, and the period in life when physical activity might reduce the risk of breast cancer (intervention studies would be the ultimate objective in future research in physical activity and breast cancer prevention)

Active smoking and exposure to environmental tobacco smoke

Gaps in our understanding of the association between breast cancer and exposure to tobacco smoke might be filled with the help of the following:

- Studies that clearly define pre- and postmenopausal women and analyze the data for these groups separately, as these subpopulations likely have different etiologies and risk factors, and tobacco smoke may affect them differently
- Detailed information on receptor status (estrogen, progesterone, and possibly others)
- Detailed biological data to determine whether or not there are any specific gene-environment interactions (e.g., genes that code for the p53 and cytochrome P-450 enzyme systems or acetylization status)

Occupational exposures

Gaps in our understanding of the association between breast cancer and occupational exposures might be filled with the help of the following:

- Use of refined indicators of occupational exposures (especially for "new" exposures such as EMF)
- Development of biological markers of exposure in the case of fugitive exposures to very reactive compounds
- Better analyses of exposure-response trends that take into account error factors inherent in retrospective exposure assessments
- Studies that focus on incidence data and rely as much as possible on histologically confirmed cases
- Studies that consider the estrogen- and progesterone-receptor status of the tumors, and always take into account menopausal status
- Exploration of substances or circumstances that may disrupt hormonal balance

Electromagnetic field exposure

Gaps in our understanding of the association between breast cancer and exposure to electromagnetic fields might be filled with the help of the following:

- More accurate sources of information on exposure
- Studies that take into account menopausal status and estrogen-receptor status
- Studies that measure all relevant confounding factors and have sufficient statistical power to detect small excess risks

Organochlorines

Gaps in our understanding of the association between breast cancer and exposure to organochlorines might be filled with the help of the following:

- Exposure assessment that measures exposure within critical time periods for breast cancer carcinogenesis rather than cumulative exposure

- Development and use of methods that examine the impact of different mixtures of organochlorines: for instance, researchers could investigate individual contaminants while controlling for others, summing the levels of contaminants in different structure-activity groups (e.g., estrogenic, androgenic, dioxin-like)
- Use of statistical techniques such as principal-components analysis to estimate the joint effects of congeners
- Use of a total toxic-equivalency approach to assess exposure to dioxin-like effects or total estrogen equivalency
- Studies of effect modifiers that influence the metabolism of organochlorines or that work in the same pathway of carcinogenesis as organochlorines: candidates for this research include polymorphisms in genes encoding cytochrome P-450 enzymes, aromatase, catechol-O-methyltransferase, estrogen receptors, and the androgen receptor
- Studies of other factors that affect the concentration of organochlorines in the body, such as body mass index, parity, and lactation history
- Studies of organochlorines and contaminants with endocrine-disrupting effects, such as tris(4-chlorophenyl)methane, tris(4-chlorophenyl)methanol, and alkylphenol ethoxylate surfactants

Emerging hypotheses and methodological approaches

Gaps in our understanding of breast cancer etiology might be filled with the help of the following:

- Studies that explore the mechanistic pathways of breast carcinogenesis, including apoptosis and factors that affect it, and the fetal antigen hypothesis
- Studies that investigate environmental and industrial substances, including plasticizers, organohalogens, heavy metals such as cadmium, PAHs, biocides, nitrosamines, chlorinated paraffins, the water disinfection byproduct MX, and styrene
- Studies that investigate exposure to pharmaceuticals, including SSRIs and tricyclic drugs
- Studies that investigate viruses, especially Epstein-Barr and mouse mammary tumor virus
- Studies that investigate group or social level determinants of breast cancer risk that may be more amenable to public health interventions
- Studies that investigate hormones, insulin-like growth factors, and subtypes and variants of receptors and binding proteins
- Methodological approaches that emphasize creative interpretation of surveillance data, animal research, and analogies made with other diseases and risk factors in generating hypotheses
- Methods that time exposures over the individual's lifetime, relative to developmental events
- Development of methods that measure exposure in early life stages
- Use of biomarkers to measure exposure more precisely
- Development of methods that measure genetic mutations and polymorphisms and permit the investigation of gene-environment interactions
- More examination of interactions between pairs of susceptibility factors and carcinogens that are biologically related
- Use of DNA microarray data to classify diseases by type
- Use of intermediate endpoints for breast cancer such as mammographic density

Biological mechanisms for breast cancer

Gaps in our understanding of biological mechanisms for breast cancer might be filled with the help of the following:

- Studies that investigate the molecular and cellular mechanisms that may be operative when individuals are exposed to EMF, PAHs, and organochlorines
- Studies that investigate the role of alcohol-derived ROS and anti-oxidants in breast cancer development
- Studies on the effect of organochlorine exposure early in life
- Studies that investigate gene-environment interactions
- Studies that use DNA microarray data to identify proteins implicated in the carcinogenesis of breast cancers
- Studies aimed at the development of novel biological markers of exposure (e.g., polymorphism in genes encoding cytochrome P-450 enzymes, catechol-o-methyltransferase)
- Studies that investigate the effect of EMF on hormonal status and genes regulating estrogens and androgens

Evolutionary etiology of breast cancer

Gaps in our understanding of the association between evolutionary biology and breast cancer etiology might be filled with the help of the following:

- Meta-analytic studies that use the best mathematical estimates of risk to analyze existing epidemiological data from an evolutionary perspective: known etiological risks must be reconsidered based on mutation rate, number of cell divisions in the breast while incorporating the changes in menarche, age at first full-term pregnancy, and so on
- Basic research on normal and induced mammary tissue differentiation: many lifestyle risks for breast cancer that we have considered non-modifiable may need to be modified (Although we cannot suggest that modern North American women bear their children in their teens, we may consider providing an endocrine signal to their breast tissue that differentiates those cells into the terminal phenotype and thereby lowers lifetime cell divisions and risk.)
- Interdisciplinary collaborations: specialists in evolutionary biology, species divergence, and natural selection in populations of unicellular organisms might work with cancer researchers to apply their models and perspectives to predicting the emergence of clinical breast cancer and the responses of cancer and precancerous cells