

**Review of the Etiology of Breast Cancer with
Special Attention to the Potential Role of Organochlorines**

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Abstract

Breast cancer is the most frequently diagnosed cancer among Canadian women, accounting for about 30% of all new cancer cases each year. Although, the incidence of breast cancer has been increasing slightly over the past 50 years, the cause of this increase is unknown. Risk factors for breast cancer can be classified into four broad categories: genetic/familial, reproductive/hormonal, lifestyle, and environmental. Established risk factors for breast cancer include older age, later age at first full-term pregnancy, no full-term pregnancies, postmenopausal obesity, and genetic factors. However, these known risk factors cannot account for the majority of documented cases of breast cancer. It has been suggested that exposure to some environmental chemicals such as organochlorines may play a causal role in the etiology of breast cancer through estrogen-related pathways. Although, the relationship between organochlorines and breast cancer risk has been studied extensively in the past decade, currently available data linking exposure to these environmental estrogens and breast cancer are equivocal. At this point, there is no strong evidence to support a causal role of organochlorines as a group in the etiology of human breast cancer. However, specific chemicals within this group, such as Mirex and PCB congeners, may be associated with increased risk.

Introduction

Apart from skin cancers, breast cancer is the most common cancer among women and is second only to lung cancer as a cause of cancer deaths among women in the developed world. The International Agency for Research on Cancer estimated that one million women worldwide developed breast cancer in the year 2000. There were about four million cases of breast cancer diagnosed during the previous five years resulting in 373,000 deaths from this disease¹.

Breast cancer incidence rates have increased gradually since the 1940s in many industrialized countries. Western Europe, the United States, and Canada have the highest incidence of breast cancer, with the lowest rates found in Asia². When women migrate from Asian and other countries with low breast cancer incidence to industrialized countries with high rates of breast cancer, their breast cancer risks gradually approach that of the host country. These findings are consistent with an important role of environmental or lifestyle factors in the etiology of breast cancer³.

In China and Japan, breast cancer incidence rates are about half those in Canada or the USA. An estimated 251,300 new cases of breast cancer in the United States and 20,700 cases in Canada diagnosed in 2002. During the past 25 years, breast cancer incidence rates in Canada have increased by approximately 28%. Current estimates suggest that about 1 in 9 Canadian women will develop breast cancer during their lifetime and about 1 in 26 women will die from this disease⁴. Recent modest reductions in breast cancer mortality rates have been attributed to earlier detection and more effective treatments.

Etiology of Breast Cancer

The known risk factors for breast cancer account for only a small proportion of all cases⁵. Such risk factors are classified here into four broad categories: genetic/familial, reproductive/hormonal, lifestyle, and environmental factors. Pre-existing breast conditions and height are also known to affect breast cancer risk.

Benign Breast Conditions

Benign breast disease (also known as fibrocystic breast disease or mammary dysplasia) is a common condition involving benign changes in breast tissue characterized by proliferation of apparently normal cells and cysts. About one-third of benign breast disease can be classified as benign proliferative breast disease, a condition associated with increased breast cancer risk⁶. Mammographic breast density also appears to be a risk factor for benign breast disease and is an independent risk factor for breast cancer⁶. A meta-analysis of epidemiologic studies showed a two- to five-fold increased risk of breast cancer among women with mammographically dense breast tissue as compared to women with less dense tissue⁷. Benign proliferative breast disease, especially atypical hyperplasia, is associated with a family history of breast cancer⁸.

Height

A pooled analysis of seven cohort studies showed positive associations between height and breast cancer risk among postmenopausal but not premenopausal women⁹.

Genetic and Familial Factors

About 5 to 10% of breast cancers in the general population have a hereditary basis¹⁰. In affected families, however, risk is particularly high if a first-degree relative has premenopausal bilateral breast cancer or two first-degree relatives have any form of breast cancer¹¹. The major known breast cancer genes, BRCA1 and BRCA2, are involved in DNA repair and transcriptional regulation. The lifetime risk of breast cancer for women who carry the BRCA1 or BRCA2 genes is about 80%; this risk is increased by late age at first birth, decreased by breast feeding, oophorectomy, and cigarette smoking¹². The impact of hormone therapy (HT) on BRCA1/2 mutation carriers is unknown. BRCA1 appears to alter the expression of several hundred genes, including some known to be associated with breast cancer (MYC, cyclin D1, STAT1, JAK1, laminin 3A, ID4, and prohormone stanniocalcin)¹³.

A recent review concluded that in addition to the high penetrance BRCA1 and BRCA2 genes, there are 13 polymorphisms in 10 genes related to breast cancer susceptibility¹⁴. For example,

women with a short polyglutamine repeat in the androgen receptor protein (occurring in about 16% of the general population) have reduced breast cancer risk¹⁵. A meta-analysis indicates associations between rare H-ras-1 alleles and increased breast cancer risk, with an estimated population attributable risk of 9%; these traits occur more frequently among African Americans than Caucasians¹⁶. A polymorphism of sulfotransferase (SULT1A1) is associated with increased breast cancer risk, particularly among women with risk factors related to high endogenous estrogen exposure (alcohol intake, high body mass index (BMI), early age at menarche, and late age at menopause). This association is consistent with reduced inactivation of endogenous estrogens by the variant enzyme¹⁷. The consumption of overcooked red meat among women with the common SULT1A1 genotypes has also been associated with increased breast cancer risk, possibly because of increased activation of heterocyclic amines in well-cooked red meat¹⁷.

Hormonal and Reproductive Factors

Estrogen and progesterone are imperative for normal mammary gland function and growth. Estrogen and progesterone interact with particular receptor proteins in the cell nucleus and can promote both proliferation and malignant transformation of breast cells¹⁸. Moreover, estrogen can be metabolically activated to cytotoxic and genotoxic products¹⁹.

Reproductive factors

Human studies support an etiologic role for estrogens in breast cancer. Several identified risk factors for breast cancer increase lifetime exposure to endogenous or exogenous estrogens²⁰. These factors include early age of menarche, late onset of menopause, not having children, late age at first pregnancy, oral contraceptive use, hormone therapy, and postmenopausal obesity (which favors conversion of androgen to estrogens in adipose tissue). A pooled analysis of six cohort studies showed associations between breast cancer and late menarche, high parity, and late age at first birth²⁰.

Endogenous hormones

Among women in prospective cohort studies, high baseline levels of endogenous estrogens (estrone, estradiol, bioavailable estradiol) and their androgenic precursors were associated with increased breast cancer risk²¹. For example, in the U.S. Nurses' Health Study, breast cancer risk increased two-fold among women in the highest quartile of endogenous estrogen levels²². Urinary estrogen levels were substantially higher among U.S. women as compared to Singapore Chinese women, paralleling the large difference in breast cancer risk between these two countries²³.

Hormone Therapy

Hormone therapy is used to increase levels of estrogen around menopause when women naturally have lower endogenous estrogen. HT increases risk of breast cancer among women who use it for at least five years, with the risk increasing by about 2.3% per year of use²⁴. Breast cancer risk varies by type of HT, and is considerably higher among those using estrogen-progestin combinations compared to estrogen alone^{25,26}. The risk of developing breast cancer by age 70 increased by 23% in women with a history of HT use between the ages of 50 to 60 compared with women with no history of HT use²⁷.

Oral Contraceptive Hormones

A pooled analysis of 54 studies (over 53,000 cases and over 100,000 controls) concluded that, compared to never-users of oral contraceptives, breast cancer risk is 24% higher among current users, and 16% higher among women who ceased use within the past 10 years²⁸. However, breast cancer risk returns to normal 10 or more years after cessation of oral contraceptive use. Breast cancers among women with a history of combined oral contraceptive use tend to be diagnosed at earlier clinical stages²⁸. Recent use of a synthetic progesterone drug (Depo-Provera) has been associated with a doubling of breast cancer risk, suggesting that the drug may accelerate growth of pre-existing lesions²⁹.

Glucose and related factors

Altered glucose metabolism has been linked to breast cancer incidence and severity. Biomarkers of increased breast cancer risk include plasma glucose, insulin and insulin-like growth factor I (IGF-I) levels. Plasma IGF binding protein (IGFBP) levels has been linked to lower risk in some³⁰ but not all studies³¹.

Lifestyle Factors

The fact that most newly diagnosed breast cancer cases are not attributable to established risk factors other than age is consistent with an important role of lifestyle and environmental factors in the etiology of the disease. This observation might also explain the wide variation in breast cancer incidence seen internationally.

Obesity and Physical Activity

A pooled analysis of seven cohort studies demonstrated that body mass index (BMI) was inversely associated with premenopausal breast cancer but positively associated with postmenopausal breast cancer, emphasizing the distinct patterns of breast cancer occurrence among younger and older women³². Few studies have assessed the relationship between weight change over time and the risk of breast cancer. One such study, involving over 10,000 postmenopausal breast cancer cases and controls, showed that weight gain since the lowest adult weight was associated with increased breast cancer risk, while the opposite held for women whose highest adult weight occurred before age 45³³. This study also showed an inverse association between postmenopausal breast cancer and frequency of strenuous physical activity between the ages of 14-22, especially among the subset of women who had also lost weight or gained little weight since age 18³⁴.

Diet

Studies of influence of diet on breast cancer risk have mainly focused on dietary fat and fruit and vegetable intakes. A recent review of diet and breast cancer reached the following conclusions³⁵.

- Detailed analyses of large prospective studies have not supported an important role for dietary fat.
- Positive energy balance, reflected in early age at menarche and weight gain as an adult, is an important determinant of breast and colon cancers, consistent with numerous animal studies.
- Physical inactivity is an important risk factor for breast cancer.
- Observed links to consumption of red meat may reflect factors other than fat.
- Compared to case-control studies, prospective studies have generally shown weaker protective effects of the consumption of fruits and vegetables against breast cancer.
- Current evidence most strongly supports a benefit of higher folate consumption in reducing risks of colon and breast cancers, particularly among persons who regularly consume alcohol.

Although meat is a major source of dietary fat with genotoxic substances produced during cooking or processing, a pooled analysis of eight cohort studies showed^{36,37}: (1) no significant associations with red or white meat and breast cancer, (2) no association with total dairy fluids or total dairy solids, (3) a slightly increased risk among women who consumed at least one egg daily, (4) a borderline association with saturated fat, and (5) no associations with monounsaturated or polyunsaturated fat consumption. There is, however, limited evidence for a protective effect of olive oil consumption³⁸ against breast cancer. Dietary fat restriction causes significantly reduced serum estradiol levels among premenopausal and postmenopausal women³⁹. The potential role of dietary fat intake during childhood and adolescence is unknown. It is possible that reduced dietary fat intake sustained from early life could reduce cumulative exposure to endogenous estrogen and thereby reduce breast cancer risk.

Although ecologic and case-control studies have suggested a protective effect of dietary phytoestrogens, notably those related to consumption of soy products, a cohort study that measured urinary levels of phytoestrogen showed only a weak inverse association⁴⁰. Dietary soy protein intake, however, was inversely related to high-risk mammographic breast parenchymal

pattern⁴¹. A pooled analysis of cohort studies revealed no significant relationships between breast cancer and intake of fruits and vegetables⁴².

Alcohol Consumption

Breast cancer risk is associated with alcohol consumption, independent of other risk factors and type of beverage, with an average excess relative risk of 9% per daily drink⁴³. Alcohol may also be a risk factor for reduced survival after breast cancer⁴⁴. A case-control study of healthy postmenopausal women showed that daily consumption of 1-2 drinks increased their serum estrone sulfate and dehydroepiandrosterone sulfate levels by about 5-10%, suggesting a possible mechanism for the observed association between alcohol and breast cancer⁴⁵.

Cigarette Smoking

Although tobacco smoke causes many human cancers and contains several known animal mammary gland carcinogens, its role in the etiology of breast cancer is not yet clearly established. There is convincing animal evidence and limited human evidence that the female breast is most sensitive to environmental carcinogens during the period between menarche and first full-term pregnancy⁴⁶. The epidemiologic evidence linking tobacco smoke and human breast cancer relates primarily to active smoking, rather than exposure to environmental tobacco smoke (ETS). In one study, breast cancer risk (all ages) has been linked to early onset (age 10-14 years) of smoking⁴⁷. Also, premenopausal breast cancer was associated with onset of smoking among parous women within 5 years of menarche and among nulliparous heavy smokers⁴⁸. Among postmenopausal women whose body mass index had increased since age 18 and who started to smoke after a first full-term pregnancy there was a reduced risk of breast cancer⁴⁸. There is mixed evidence of an association between breast cancer and ETS exposure with positive findings in some^{49,50,51} but not all studies^{52,53}; a meta-analysis of 11 epidemiologic studies yielded a combined relative risk estimate of 1.43 (CI 1.10-1.85)⁵⁴.

Environmental Factors

Occupational Exposure

There is limited evidence to suggest that breast cancer risk may be increased among women in certain occupations, including dental hygienists, nurses, teachers, beauticians, airline attendants, laboratory technicians, telephone and telegraph operators, leather and fur processors, glass-manufacturing workers, and metal fitters and assemblers⁵⁵⁻⁵⁷. Specific occupational exposures linked to breast cancer include organic solvents⁵⁸ and ionizing radiation⁵⁹. Both organic solvent exposure and exposure to ionizing radiation have been shown to be carcinogenic in highly-exposed humans and experimental animals^{60,61}.

Ionizing Radiation

High exposures to ionizing radiation related to medical diagnosis or treatment is a known cause of breast cancer⁶⁰. Women with benign breast disease or a family history of breast cancer may have increased breast cancer risk following relatively low-level exposure to ionizing radiation⁶¹.

Electromagnetic Fields

A review of epidemiologic studies of breast cancer and power-frequency electromagnetic fields (EMF) concluded that: (1) among 11 studies of occupational EMF exposure, there were significant associations with breast cancer in most of these studies, and, (2) among 8 studies of residential EMF exposure and studies of electric blanket exposure, results were inconsistent, most showing no significant relationships⁶².

Environmental Contaminants

There is considerable scientific and public interest in the possible role of environmental contaminants in the etiology of breast cancer, particularly those with alleged estrogenic activity such as specific organochlorines. These chemicals include DDT, its metabolites, several other pesticides, and polychlorinated biphenyls (PCBs). Chemicals known to cause mammary gland tumours in animals include solvents (benzene, methylene chloride, 1,1- and 1,2-dichloroethane), pesticides (dichlorvos) and therapeutic drugs (reserprine). Many environmental contaminants

such as DDT and its metabolites cause other types of cancer in experimental animals⁶³. Epidemiologic studies of breast cancer risk and environmental contaminants vary from ecologic (correlative) studies with no individual exposure information to cohort and case-control studies that measured indices of internal dose such as blood or breast adipose tissue organochlorine levels.

Polychlorinated biphenyls (PCBs)

Some epidemiologic studies have shown associations between serum or plasma PCBs and breast cancer⁶⁴⁻⁷⁰ while others have not⁷¹⁻⁷⁸. In some studies, associations were only apparent in subgroups (e.g., among African-American but not white women⁷⁹). In one study, certain congeners were positively associated with breast cancer while others were inversely related⁸⁰. Given that breast adipose tissue PCB levels and congener profiles differ from those in blood and occur in the target site of interest, they may provide the best available exposure index. Studies using breast adipose tissue measurements have demonstrated the following results.

- A Swedish case-control study showed positive but imprecise associations between postmenopausal breast cancer and breast adipose tissue levels of coplanar but not non-coplanar PCB congeners⁸¹.
- An Ontario case-control study showed associations with breast adipose tissue levels of PCB congeners, particularly congeners 105 and 118 among premenopausal women and with congeners 170 and 180 among postmenopausal women⁸².
- A case-control study in Connecticut showed no association with breast tissue PCB levels⁸³.
- A case-control study in Long Island showed an association with congener 183 but not with other or total PCB congeners⁸⁴.
- A small case-control study in Wisconsin found no associations with tissue levels of any of 18 PCB congeners⁸⁵.

Given their methodological strengths, longitudinal cohort studies provide an important source of information on breast cancer risk. Cohort studies have relied exclusively on stored serum PCB measurements and have generally not shown significant, positive associations^{73,76}. Two cohort studies have suggested possible associations between PCBs and breast cancer risk^{65,67}. In one study, there was a borderline positive association among women monitored less than three years

before breast cancer diagnosis⁶⁵. The most convincing cohort study collected blood samples twice, five years apart, and showed borderline or significant associations between breast cancer and average serum levels of total PCBs, PCB-118 and PCB-138. A recent extension of this study revealed a suggestive but statistically non-significant association between breast cancer and serum total PCBs among the subgroup with mutant p53 breast cancers (OR=3.00, 95% CI 0.66-14.0)^{66,67}.

Several studies of experimental animals exposed to PCBs have shown increased mammary gland cancer risks. Prenatal and lactational exposure to relatively low levels of PCB-126 caused increased rates of DMBA (dimethylbenz (a) anthracene) induced cancers in rats⁸⁶. PCB-77 markedly enhanced the development of DMBA-induced mammary tumors in young female rats⁸⁷. In contrast, rats exposed to commercial PCB mixtures had reduced incidence of mammary tumors⁸⁸.

In summary, there is limited evidence on which to base a conclusion regarding the role of PCBs in the etiology of breast cancer. More and larger studies need to be conducted since those that exist often lack statistical power and have reached inconsistent conclusions. At this time, several studies suggest that specific PCBs could cause breast cancer, a conclusion that has some biological plausibility. However, the epidemiological evidence is not sufficiently strong to support the general conclusion that PCBs cause human breast cancer. Two studies have also suggested that specific PCBs could be associated with more aggressive tumors^{64,94}. There have been few studies of the potential role of polymorphisms in breast cancer risks related to organochlorines and it is possible that certain subgroups in the population may be more susceptible to the effects of these environmental exposures. Also, the potential for interactions between PCBs and other exposures such as tobacco smoke remains unexplored.

ρ,ρ'-DDE and ρ,ρ'-DDT

Developed early in World War II as the first modern insecticide, DDT was initially used to combat malaria, typhus and other insect-borne human diseases among military and civilian population⁸⁹. Before the United States banned DDT in 1972, 675,000 tons were used domestically in agriculture and commercial applications, with a peak use of 40,000 tons in 1959.

DDT is a complex mixture of several DDT congeners, the most estrogenic being o,p'-DDT (about 15-23% of the mixture)⁸⁹. The main congener, p,p'-DDT, forms about 77% of the mixture and degrades to p,p'-DDE, the most prevalent and persistent metabolite in the environment; p,p'-DDE has anti-androgenic but little estrogenic activity⁹⁰.

Although some small epidemiologic studies showed limited evidence of an association between breast cancer and serum or adipose tissue DDE levels, the first large-scale well-designed study to show a positive association was a nested case-control study conducted within a cohort of over 14,000 women in the New York University Women's Health Study⁹¹. This study showed an association between serum DDE at baseline during 1985-91 and breast cancer (adjusted RR=3.7, 95% CI 1.0-14, for a 10th to 90th decile increment in serum DDE levels). Subsequent epidemiologic studies have generally shown no consistent association between serum or adipose tissue DDE levels and breast cancer^{70,72,73,74,76,77,78,82,85,92}. A pooled analysis of five case-control studies (1,400 cases, 1,642 controls) conducted in the northeastern United States showed no association between breast cancer risk and p,p'-DDE (OR = 0.99, 95% CI 0.77-1.27)⁹³. Other studies have demonstrated associations between plasma p,p'-DDE and lymph node invasion⁶⁴, a relatively strong association between serum p,p'-DDE and postmenopausal breast cancer in a Mexican study, and a borderline association between breast adipose tissue p,p'-DDE levels and ER (estrogen receptor)-negative breast cancer⁹⁴.

A recent review of epidemiologic studies of breast cancer and DDT/ DDE noted that the main DDT-related exposure during recent decades in United States involved dietary p,p'-DDE rather than the far more estrogenic o,p'-DDT present in DDT spray⁹⁵. This review concluded that there were no consistent associations between serum DDE levels and: (1) breast cancer in United States, (2) breast cancer in Colombia, Mexico or other countries with more recent DDT use than United States, (3) breast cancer stratified by premenopausal vs. postmenopausal status or by lactational history, or (4) breast tumor size, stage, or metastatic potential.

The International Agency for Research on Cancer concluded that there is sufficient evidence that DDT and its metabolites cause cancer in animals, including liver and lung cancers and lymphomas. Rats exposed as neonates to dioxin or to a mixture of DDT, DDE, and 19 PCBs

found in human breast milk, but at 1000-fold higher concentrations, followed by a single injection of methylnitrosourea (MNU) developed more benign and malignant breast tumors than those exposed to MNU alone⁹⁶.

Other organochlorine compounds

There have been relatively few studies of associations between breast cancer and serum levels of other organochlorine compounds including the following chemicals.

Mirex: A borderline association between breast cancer risk and Mirex was found among subgroup of parous women who had never lactated⁷⁰; this hypothesis was tested and supported in a subsequent study⁸².

Hexachlorobenzene (HCB): Two case-control studies found no association between HCB and breast cancer^{65,75}, while a nested case-control study showed a positive association, but only among women sampled less than three years before breast cancer diagnosis⁷⁰.

Dieldrin: An elevated, although non-significant, risk of breast cancer was associated with exposure to dieldrin in a Long Island case-control study⁷², along with a suggestive association among women with mutant p53 breast cancers in a Danish nested case-control study (OR=3.53, 95% CI 0.79-16, 4th vs. 1st quartile of serum dieldrin)⁶⁶. The latter study also showed an association between serum dieldrin levels and reduced survival of incident cases (RR=2.61, 95% CI 0.97-7.01)⁶⁷.

Chlordane: No association with incident breast cancer was found in two studies^{72,77}, although another study reported an association with lymph node invasion⁶⁴.

TCDD: A borderline association between serum TCDD levels and breast cancer risk was observed among women exposed during the Seveso incident (RR = 2.1, 95% CI 1.0-4.6, for a 10-fold increase in serum TCDD levels)⁹⁷. TCDD is a potent animal carcinogen, causing cancer (usually at multiple sites) in all species tested at doses as low as 1 ng/kg/day. Rats exposed parentally to a single low dose of TCDD develop more mammary gland terminal end buds⁹⁶, the

breast structures most susceptible to carcinogenesis; such animals are more susceptible as adults to chemically-induced breast cancer.

Other organochlorine pesticides: A population-based case-control study showed associations between aggressive breast cancers and plasma β -hexachlorocyclohexane, p,p' -DDE, oxychlordan and transnonachlor levels⁶⁴. Other case-control studies showed no association with serum β -hexachlorocyclohexane and an imprecise increased odds ratio for breast adipose tissue β -benzene hexachloride levels (OR=3.1, 95% CI 0.6-15, 3rd vs. 1st tertile) among the subgroup of nulliparous women⁹⁸. An ecologic study in Kentucky showed a weak association between breast cancer incidence rates and contamination of drinking water by triazine herbicides⁹⁹. A large case-control study in North Carolina showed associations with pesticide exposure indices¹⁰⁰.

Other Environmental Contaminants

Polycyclic aromatic hydrocarbons (PAHs): Although well studied as mammary gland carcinogens in rodents, the potential role of PAHs in human breast cancer remains largely unexplored. PAH-DNA adducts in blood lymphocytes or breast tissue has been associated with breast cancer in case-control studies, independent of known breast cancer risk factors, current active and passive smoking, and dietary PAH^{101,102}.

Disinfection by-products: Although a Finnish ecologic study showed a weak association between breast cancer and mutagenicity of chlorinated drinking water¹⁰³, a U.S. case-control study showed no relationship with chlorine dose¹⁰⁴.

Conclusion

Known risk factors for breast cancer include age, early onset of menstruation, later age at menopause, later age at first full-term pregnancy, no full-term pregnancies, alcohol intake, postmenopausal obesity, hormonal therapy, hormonal contraceptives, ionizing radiation, benign proliferative breast disease, mammographic breast density, and genetic/familial factors. Possible factors that could increase risk include environmental tobacco smoke and cigarette smoking, no history of breast-feeding and lack of physical activity. The causes of most breast cancer cases

remain unknown. The large geographic differences in risk have focused concern on the potential role of environmental factors and lifestyle. However, at this time there is insufficient evidence to support a strong role for organochlorines in the etiology of human breast cancer, despite the fact that there is considerable biologic plausibility for a role of some of these exposures. At the same time, specific pesticides such as Mirex and chlordane, and specific PCB congeners, do exhibit increased breast cancer risk or associations with more aggressive breast tumors in the few studies that have included these substances. Methodologic challenges in this area of research, such as the possibly long latency period between exposure and tumor development, and the difficulty in obtaining quantitative and precise measure of past exposures, may account for the limited and inconsistent evidence from epidemiologic studies. The diversity in study designs, particularly in exposure indices, and the low statistical power (because of small sample size and/or low proportion of highly exposed individuals) also contribute to the generally inconsistent findings in this area.

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