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Perspective

Perspectives of breast cancer etiology: synergistic interaction between smoking and exogenous hormone use

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Abstract

To explore breast cancer etiology, literature was searched using Medline. We explored the (1) plausibility of smoking in breast carcinogenesis; (2) physiological properties, susceptibility windows, and exposure timing of breast cells; (3) role of exogenous hormones in breast carcinogenesis; (4) biological mechanism of synergistic interactions between smoking and exogenous hormones in breast carcinogenesis; and (5) evidence from epidemiologic studies and the fitted secular trend between smoking rate, exogenous hormone use, and breast cancer incidence in past decades. We deduced that exogenous hormone use per se is not a significant cause and its association with breast cancer is distorted by chronic exposure to environmental carcinogens, especially smoking. We hypothesize that smoking is one of the causes of breast cancer and that this causality is strengthened by synergistic interaction between smoking and exogenous hormone use. Physicians should be cautious of prescribing exogenous hormones for those with chronic exposure to environmental carcinogens to prevent breast cancer.

Key words Breast cancer etiology, smoking, exogenous hormone use, synergistic interaction, mechanism

Worldwide, breast cancer incidence, which ranks first among all cancers since the 1990s, continues to rise in all age groups, most rapidly in low-risk populations [1,2]. However, the cause of increased risk of breast cancer in the past several decades is not completely understood. About 90% to 95% of breast cancers are sporadic and occur in women without inheritable genetic mutations such as *BRCA-1* and *BRCA-2* [3,4]. A twin study shows that about two-thirds of breast cancers appear to have a non-genetic origin [5]. Thus, increased interest has been paid to the roles of environmental factors in breast cancer etiology in recent years[6]. No single environmental factor is confirmed to be a cause of increased risk of breast cancer. Smoking is an important environmental factor proposed to contribute to a partial increase in breast cancer risk in the past decades [7-10]. Exogenous hormone use is also suspected to contribute to a partial increase in breast cancer risk since the Women's Health Initiative (WHI) study [11]. Based on the results of a literature search and review, we hypothesize that there are synergistic interactions between smoking and exogenous hormone use in the etiology of breast cancer.

Literature Search Strategy and Criteria

Literature was searched using Medline via PubMed. The following search terms were used: breast cancer, etiology, risk factors, smoking, active smoking, passive smoking, secondhand smoke, oral contraceptive (OC), and hormone replacement therapy (HRT). Additional articles were identified through references, reviews, and organization summary documents. Any publication supported directly by the tobacco industry was excluded due to expected bias. Originally, a total of 163 references

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were screened out. Due to space and citation limitations, reviews, meta-analysis articles, and organization summary documents, such as the International Agency for Research on Cancer (IARC) Monograph and Surgeon General's Report, are cited instead of individual articles if those individual articles were cited in these organization documents. Since this literature review was finished before 2007, some individual articles published after 2007 may not be cited if there were no new scientific points added and because so many papers have been published in recent years.

Smoking and Breast Cancer

Tobacco smoke contains at least 87 human carcinogens (*Group 1*) and 63 probable human carcinogens (*Group 2A*)[12]. Animal experiments and *in vivo* studies have shown that these compounds found in tobacco induce mammary tumors[13]. Smokers have a higher prevalence of smoking-specific DNA adducts and *p53* gene mutations in breast tissue than nonsmokers[14].

Carcinogens from tobacco smoke can be transported to the breast via plasma lipoproteins after passing through the alveolar membrane and into the blood stream[13]. Because they are lipophilic, tobacco-related carcinogens can be stored in breast adipose tissue and then metabolized and activated by human mammary epithelial cells[13]. Metabolites of tobacco smoke have been found in the breast fluid of smokers[15-17]. Thus, the biological plausibility of tobacco smoke in breast carcinogenesis is evidenced.

Epidemiologic studies, however, have not consistently shown active smoking to be associated with increased breast cancer risk[18,19]. A common explanation for this inconsistency is inaccurate assessment of exposure in previous studies biasing the results to the null between active smoking and breast cancer, as some studies have not investigated or have not excluded the effect of secondhand smoke in the control group[12]. Attention is needed to accurately assess exposure to secondhand smoke. Therefore, to investigate the relationship between breast cancer and secondhand smoke is necessary.

Secondhand smoke has been recognized as an important indoor environmental pollutant since the 1970s and has been classified as a human carcinogen since 1986[18,19]. The 1986 National Research Council (NRC) report on secondhand smoke indicates that some carcinogens, including at least 10 polycyclic aromatic hydrocarbons (PAHs), N-nitrosonornicotine (NNN), 4-(methylnitrosamino-)-1-(3-pyridyl)-1-butanone (NNK), and benzene, are emitted at concentrations as ten-fold high in side-stream as in mainstream smoke, but the concentrations are quickly diluted by circulating air[12]. It is well established that secondhand smoke is a complex mixture of several thousand compounds combined from exhaled mainstream and side-stream smoke, as well as compounds that diffuse through cigarette paper[19]. Its exposure pattern differs from active smoking quantitatively and, to some degree, qualitatively[12,20,21].

In epidemiologic studies, the causality between secondhand smoke and breast cancer remains inconclusive due to the lack of evidence of causality between active smoking and breast cancer[12,18,19]. The Monograph of the 2004 International Agency for Research on Cancer (IARC)[18] summarized that secondhand smoke is not a cause of breast cancer since the relationship between active smoking and breast cancer has not been conclusively shown based on epidemiologic studies before 2004. In 2005, California/Environmental Protection Agency/Office of Environmental Health Hazard Assessment (Cal/EPA/OEHHA)[12] concluded that "Epidemiologic studies, supported by animal data, provide evidence consistent with a causal association between secondhand smoke exposure and breast cancer in humans, which appears stronger for pre-menopausal breast cancer," since many but not all studies assessing the association between secondhand smoke and breast cancer have reported a positive and often statistically significant association[18,19]. In 2006, the Surgeon General's Report[9] summarized that "the overall evidence is mixed and does not strongly or consistently support a causal relationship between secondhand smoke and breast cancer. With regard to biologic plausibility, involuntary smoking would be expected to expose breast tissue to the carcinogens in secondhand smoke, as would active smoking" and concludes that the evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer based on current epidemiologic studies.

The risk of breast cancer for smoking (both active smoking and contact with secondhand smoke) appears to vary by factors such as menopausal status and timing of exposure[8,12,22]. In addition, recent reports provide evidence that breast cancer risk from smoking may be modified by other factors including the hormone receptor status of the tumor[23], metabolite enzyme genes[24-27], familial history of breast cancer[6], and exogenous hormone use[8,28].

To reconcile the discrepant findings, epidemiologists have paid increasing attention to accurate assessment of exposures to smoking carcinogens including both secondhand smoke and active smoking, to aspects of the smoker that might modify the association between smoking and breast cancer risk, and to the potentially different associations that might exist with different types of breast tumors, such as those with and without estrogen or progesterone receptors[12]. Therefore, the

association between smoking and breast cancer is possibly modified by other factors such as exogenous hormones. The following points explain how factors may modify the association between smoking and breast cancer.

Physiological Properties, Potential Windows of Susceptibility, and Timing of Exposure to Smoking Carcinogens of Breast Cells

The breast is a vital part of reproduction in human females. It reaches its fully differentiated state only through hormonal stimuli induced by pregnancy and lactation, resulting in the period between menarche (breast cells start proliferation and differentiation mainly by estrogen) and age at first parity (breast cells achieve full differentiation mainly by progestin) with increased susceptibility to carcinogens [6]. Experimental and epidemiologic studies have already shown that hormonal environment plays a critical role in the development of breast cancer [29]. Removal of both ovaries reduces risk, and increased risk has been observed for women with abnormally higher levels of estrogen[6]. Thus, reproductive factors, such as menarche, age at first parity, and age at menopause in a woman's life, seem to be involved in breast cancer development.

Epidemiologic studies of radiation and breast cancer risk provide some evidence that risk for breast cancer associated with environmental factors may vary by age at exposure. The risk of radiation-related breast cancer is substantially higher among women exposed during childhood or adolescence than among women at older ages. There seems to be a general pattern of a decline in dose-specific excess relative risk with increasing age at exposure[30]. As a modifier of radiation risk, age at first parity seems more important than menarche and age at menopause in the etiology of breast cancer. Therefore, the effect of smoking, like radiation, on breast cancer may also be modified by age at exposure and reproductive age. Studies of the timing of exposure to smoking carcinogens relative to menarche, age at first parity, and age at menopause might provide further insight into the nature of the association between cigarette smoking and breast cancer[13].

Possible modifications by only endogenous hormone-related factors on the association between both active smoking and secondhand smoke and breast cancer may not be sufficient to explain the increased risk of breast cancer in past decades. A positive association with smoking before age at first parity (before the age of 17) was found in the Nurses' Health Study [31]. We explored the effect of these endogenous hormone-related factors on the association between secondhand smoke and breast cancer in detail[8,22]. Based on our preliminary data, breast cancer risk tended to be significantly higher among pre-menopausal than among post-menopausal women and among women with early menarche, late age at first parity, and late age at menopause than among women with late menarche, early age at first parity, and early age at menopause. However, when stratified by secondhand smoke exposure level (< 2 and $\geqslant$ 2 h per day) and exposure duration (< 25 and $\geqslant$ 25 years), menopausal status, menarche, age at first parity, and age at menopause were not significantly associated with breast cancer risk. Greater biological sensitivity to endogenous hormones for breast cells may provide a milieu for interactions between exogenous hormones and environmental carcinogens.

It is possible that prenatal (sperm, egg, and uterus), postnatal, childhood, adolescent, and adult exposure to tobacco smoke up until the delivery of a woman's first child is a crucial component affecting risk of breast cancer from this exposure. As shown in Figure 1, women can be exposed to secondhand smoke anytime during their lifetime, including prenatal exposure via sperm, egg, and uterus, and women can smoke at the earliest from adolescence. How much difference exposure before childhood would make in breast carcinogenesis is not clear.

Epidemiologic studies do not fully explore the possibility that women who start exposing to tobacco smoke between menarche and first parity have a higher risk of breast cancer[32-34]. Endogenous hormones *per se* are neither sufficient nor necessary to cause significantly increased risk of breast cancer because breast cancer incidence was very low before the 1950s worldwide. However, exogenous hormones mimicking endogenous hormones have been used for women with a much higher dose than endogenous hormones since 1950s, and it is reasonable to hypothesize that exogenous hormones provide a high hormone environment for environmental carcinogens in breast carcinogenesis.

Exogenous Hormones

Oral contraceptive (OC) use and HRT are the two main sources of exogenous hormones. Both contain estrogen and/or progestin. Early OCs are synthetic compounds. In the 1990s, OCs were natural extracts taken from pregnant horses. From the late 1950s to the 1980s, the usage doses of OCs decreased, from 0.15–0.23 mg to 0.035 mg estrogen and from 10 mg to 0.5 mg progestin in one OC pill, due to severe side effects[35]. The routine dosages of 0.625 mg/day estrogen and/or 2.5 mg/day progestin were used in HRT in several trials including the WHI Hormone Trials in the 1990s [36]. HRT and other exogenous hormone use in

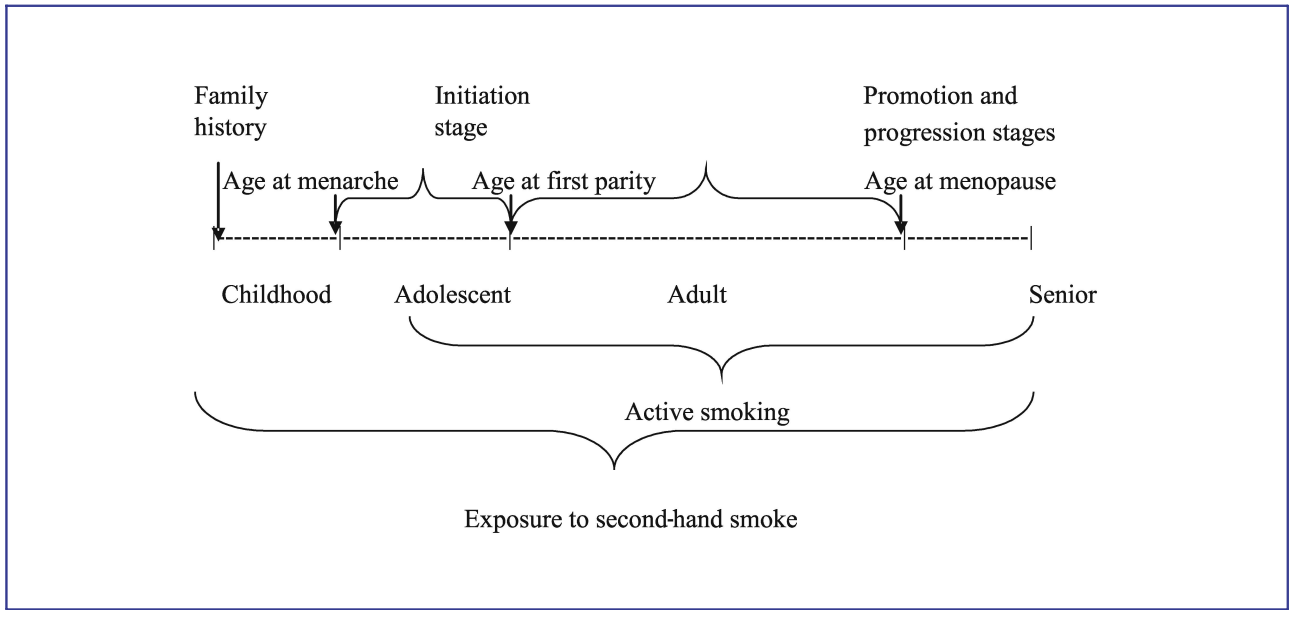

Figure 1. **Susceptible windows of breast cells and timing of exposure to tobacco smoke in breast carcinogenesis.** Potentially distinct susceptible windows (including before childhood, childhood, adolescence, adult before first parity, between first parity and menopause, and after menopause, and senior) of breast cells and timing of exposure to environmental carcinogens, such as lifetime exposures to second-hand smoke including before birth, and active smoking maybe starting during adolescence, over different breast carcinogenesis stages (cancer initiation, promotion, and progression stages) and at different ages in a woman's life.

clinics overall provide a higher dose of estrogen and progestin than OC pills.

From *in vitro* experiments, estrogen has convincingly been found to stimulate breast cancer cell proliferation although the effects of progestin are still controversial in the literature [35,37]. A recent study found that progestin not only stimulates proliferation but also inhibits cell death in human breast cancer cells [37]. Many recent large-scale clinical studies of HRT have strengthened the idea that progestin, in general, may stimulate breast cancer. Schairer *et al.* [38], in a study involving 46 355 post-menopausal women that compared HRT involving estrogen and progestin combination pill (combined HRT) to estrogen alone, found that the risk of breast cancer increased 8% per year for combined HRT as compared to 1% per year for estrogen alone. This finding seems confirmed by other studies [39,40]. However, the association between exogenous hormone use and breast cancer is still controversial in epidemiologic studies.

These exogenous hormones increase the serum hormone level in women who continuously take OCs for contraception or HRT for a long time, and then potentially stimulate breast cell proliferation including some mutated breast cells originally initiated by environmental carcinogens. To some degree, exogenous hormones act like a duplicator that duplicates breast cells including mutated cells and speeds cancer formation in the breast. Exogenous hormone use *per se* may not be a significant cause of increased risk of breast cancer in past decades [41].

Biological Mechanism of Synergistic Interaction Between Smoking and Exogenous Hormones

The potential mechanism of smoking in breast carcinogenesis may be interacted by host factors. The interaction could be (1) interactions between smoking carcinogens and genes, such as *CYP1A1* (genes specifying enzymes important in PAH metabolism) and N-acetyltransferase 2 (*NAT2*) [25-27,42,43]; (2) gene-gene interactions noted in smokers, with certain combined *CYP1A1*- and *GSTM1*-null polymorphisms having much higher levels of DNA adducts than either individually; and (3) multiple interactions between tobacco carcinogens, other environmental carcinogens, and multiple host genes in the etiology of breast cancer [44]. Therefore, we hypothesize that environmental carcinogens, such as smoking, initiate breast cancer and this causality synergistically interacts with exogenous hormones in breast carcinogenesis.

A schematic description of the potential synergistic interaction between smoking and exogenous hormone use on breast cancer is proposed in Figure 2. Smoking is known to induce hepatic cytochrome P450 (CYP) enzymes, especially the CYP1A2 enzyme in human

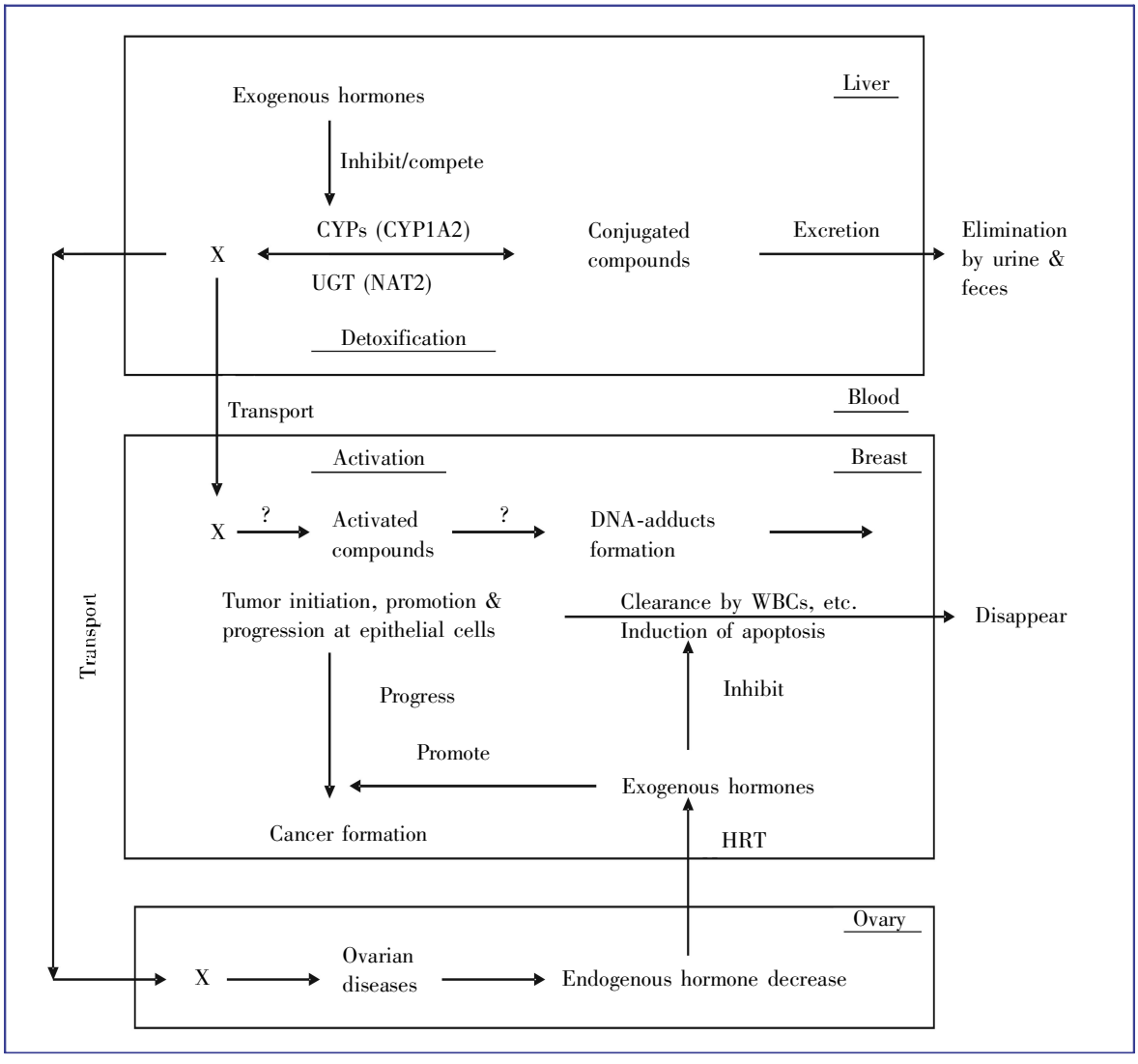

Figure 2. **Proposed biological mechanism of breast cancer carcinogenesis induced by smoking and modified by exogenous hormone use.** Detoxification: hepatic cytochrome P450 (CYP) enzymes and other non-P450 enzymes, such as uridine diphosphate glucuronosyltransferase (UGT) and N-acetyltransferase-2 (NAT2), detoxify X (representative of smoking carcinogens) in the liver and form X-OH (C-hydroxyl compound) and X-Gluc (N-glucuronide conjugated compound) or X-COCH3 (N-acetyl conjugated compound), which is eliminated by urine and feces[46,47]. Exogenous hormones inhibit[48] or compete with the CYP enzymes because exogenous hormones need the hydroxyl enzymes to eliminate them in the liver and impede the detoxification of smoking carcinogens. These compounds remain in the blood for a long time and have a high chance to be transported to breast tissue, where they would be activated by heretofore unknown N-hydroxyl enzyme in breast epithelial cells to X-OH (N-hydroxyl compound) and then form $X\text{-}OSO_3^-$ (O-glucuronide conjugated compound). This resultant compound would then have the ability to combine with DNA and initiate mutations in breast epithelial cells. Exogenous hormones promote mutated cell proliferation, inhibit the apoptosis of cancer cells, and may synergistically cause breast cancer[36]. Smoking could cause ovarian diseases and, as a consequence, ovarian function disorder. Some women could take hormone replacement therapy (HRT) and some could not. This increases the complexity of smoking carcinogens in the etiology of breast cancer. Finally, breast mutated cells progress towards immortality.

livers[45]. Smoking carcinogens are detoxified by CYPs and/or NAT2 enzymes and eliminated from the body[25,26,46,47]. However, Exogenous hormones, such as OCs and other female hormones, also need metabolic enzymes-products of metabolic genes such as *CYP1A1* and *CYP1A2*[48] to detoxify. Hormones, either endogenous or exogenous, still need CYPs (probably hydroxyl enzymes) to eliminate them in the liver. Thus, smoking carcinogens may not be cleared quickly and could remain in the serum for a long time, increasing their chance of being transported to breast tissue. Then these carcinogens would be metabolized in breast epithelial cells and activated by N-hydroxyl enzymes to hydroxyl-conjugated compounds which can combine with

DNA and cause breast epithelial cell mutations (initiation, promotion, and progression) [6]. The exact enzymes involved in this process are still unknown. When mutated cells are formed, the body's immune system would be initiated to capture them, or anticancer agents would induce them to apoptosis and make the mutated cells disappear [49]. Progestin can inhibit apoptosis of breast cancer cells. Both estrogen and progestin can stimulate breast cell (both mutated and normal cells) proliferation and cause breast lobular proliferation [37,38]. Eventually, mutated breast cells could progress to become immortal if these cells continuously expose to smoking carcinogens and or other environmental carcinogens. Furthermore, smoking causes ovarian diseases and, as a consequence, lowers endogenous hormone levels due to ovarectomy[50], which would differentially cause affected individuals to use HRT or suffer loss of ovarian function. Thus, exogenous hormones act like either a duplicator or accelerator in the causality between smoking and breast cancer. Finally, these two factors synergistically cause increased risk of breast cancer. In fact, this mechanism might explain why many random clinical trials (RCTs) like WHI failed in the past, showing null or opposite results such as a higher rate of diseases among intervention groups than control or placebo groups. This may also provide a partial explanation of why breast cancer incidence, worldwide, increased steadily and continuously in the past several decades[6].

Epidemiologic Studies

In our study on preliminary data of 396 women diagnosed with primary breast cancer during the follow-up period between 1997 and 2003 from a population-based prospective cohort of 74 942 women aged 40 to 70 years old (the Shanghai Women's Health Study), we found breast cancer was significantly associated with secondhand smoke, and this association was significantly synergistic with either OC use or other exogenous hormone use in Shanghai women [8,22]. Compared to neither active smoking nor exposure to secondhand smoke during a lifetime (common reference), the association between active smoking and breast cancer interacted synergistically with OC use ($P_{interaction}$ = 0.10) and with both OC use and reproductive diseases (RD) ($P_{interaction}$ = 0.04) although analyses were based on 6 cases who had active smoking. Furthermore, the hazard ratios (HRs) of breast cancer were 1.02 (0.73–1.43), 1.42 (0.93–2.16), and 1.72 (1.07–2.76), respectively, for average exposures to secondhand smoke of < 2, 2 to < 4, and ⩾ 4 h per day, P trend < 0.0001 compared to a common reference. The association between secondhand smoke and breast cancer interacted synergistically with OC ($P_{interaction}$ = 0.03) and other female hormone use ($P_{interaction}$ = 0.01). A multiple interaction was found between secondhand smoke, menopausal status, and other female hormone use ($P_{interaction}$ = 0.02). However, OC [HR= 0.52 (0.22–1.25)] or other female hormone [HR= 0.80 (0.31–2.10)] use per se among women never exposed to secondhand smoke seemed protectively but insignificantly associated with breast cancer.

A protective effect of OC use on breast cancer has been reported in a Turkish study [51]. A synergistic interaction between smoking and hormone use on the risk of breast ductal carcinoma *in situ* was reported by Kabat *et al.* [28]. Many RCTs have reported that the treatment group receiving either nutrients or HRT for a long time had no decrease in cancers, or even an increase in cancers or other diseases compared to control/placebo groups [52]. For example, an RCT on low-dose aspirin in the primary prevention of cancer in the Women's Health Study found that the average 10-year intervention of 100 mg aspirin does not lower risk of total, breast, colorectal, or other site-specific cancers [53]. It could be interpreted that the potential beneficial effects of nutrients or HRT or other medicines on chronic diseases including cancers may be negated by some common risk factors such as smoking. It is important for future research to look at the potential interactions between smoking and any long-term use of nutrition supplements and pharmaceuticals.

Comparison of the Fitted Secular Trend of Smoking Rate, Exogenous Hormone Use Rate, and Breast Cancer Incidence in the Past Several Decades for the USA and China

The widespread introduction of exposure to OCs and smoking carcinogens in women matched the timing of increased risk of breast cancer in the world. Women started to use OCs during the mid-1950s in clinical trials. The U.S. Food and Drug Administration approved the first OC for marketing in 1960. OCs were commonly used for contraception in the USA by 1965. The rapid increase in smoking prevalence among women began in the late 1940s and 1950s in North America [54]. The incidence of breast cancer in the USA continuously increased between the 1970s and the late 1990s and has stayed at a high level until now compared to eastern countries such as China[18].

The China Ministry of Health approved the first OC in 1961. Women who lived in urban areas started to use OCs for contraception in the late 1960s, but the usage rate was low in urban areas compared to that among American and European women. Women in rural areas of China do not use OCs. Although women in China

rarely smoke, they do have a history of high exposure to secondhand smoke. The incidence of breast cancer slightly increased in the late 1970s and sharply increased in the 1980s until now in urban areas but not in rural areas[55].

Comparing the timing between exposures to smoking carcinogens, the usage rate of exogenous hormones, and the increased incidence of breast cancer, it is possible that exogenous hormones could play a role in modifying the effect of smoking on breast cancer. Considering that breast cancer incidence in general is much less than 1%, with the worldwide highest age-adjusted incidence in North America, Northern Europe, and Australia ranging from 75 to 92 per 100 000 women per year, a significant increase in a small group of women who are exposed to any environmental carcinogens, including smoking, secondhand smoke, and routine drugs, should be counted as a contribution to the significant increase in breast cancer risk in the population. Therefore, it is reasonable to hypothesize that the synergistic interaction between smoking and exogenous hormone use on breast cancer is a cause of increased risk of breast cancer worldwide in the past decades.

Future Research Directions

The following points should be considered in future epidemiologic studies of tobacco smoke and other environmental factors in the breast cancer etiology. In the study design stage, accurate assessment of lifetime exposure to smoking carcinogens, including both active smoking and exposure to secondhand smoke, time of starting and stopping exposure, duration of exposure, and exposure levels, should be considered. Assessment of chronic exposures to other environmental carcinogens and related detoxification/metabolism enzyme genes should also be considered when assessing the association between tobacco smoke and breast cancer risk because other environmental factors including routine drugs may compete with liver enzymes with smoking carcinogens during detoxification. And *vice versa*, when assessing the association between other environmental factors and breast cancer risk, smoking, routine drugs, and related detoxification/metabolism enzyme genes should be considered. In addition, accurate assessment of breast cancer including histopathologic information, such as estrogen and progesterone receptors and related mutated genes, should be considered.

During the data analysis stage, a group with no or relatively low secondhand smoke exposure should be considered as a control group for all variables of exposure to smoking carcinogens. Otherwise, the results will be biased to the null. Furthermore, all potential interactions between smoking carcinogens and other environmental factors including OC use, HRT and other routine drugs, and related metabolic genes should be considered.

During the data interpretation stage, any significant interactions between environmental factors such as smoking, exogenous hormones, and related metabolic genes should not be neglected, even if they occur in a small group of women.

Finally, potential biological mechanisms of the interactions between smoking and other environmental factors and related metabolic genes should be investigated in the etiology of breast cancer.

Conclusions

In the absence of a causal relationship between the occurrence of sporadic breast cancer and inheritable gene mutations, the contribution of environmental factors and interactions between them, as well as related metabolic genes should be continuously and extensively investigated. A possible biological mechanism of smoking in breast carcinogenesis and synergistic interactions between smoking carcinogens and exogenous hormones is proposed in Figure 2. Evidence indicates that exogenous hormone use *per se* is not a significant cause of breast cancer; however, smoking is at least one of the causes of breast cancer, and this causality may be strengthened by the synergistic interaction between smoking and exogenous hormones involving related metabolic genes. Furthermore, exogenous hormones act like a duplicator or accelerator in this causality, though this relationship may be complicated by factors related to endogenous hormones. Although exogenous hormone use *per se* is not a cause for breast cancer, physicians should be cautious of prescribing exogenous hormones for those with chronic exposure to environmental carcinogens, including smoking, in order to prevent breast and other cancers.

This review provides a hypothesis for why breast cancer incidence has increased steadily and continuously in past decades and why many RCTs on HRT, beta-carotene, and other nutrient supplements found null results or even a higher rate of disease among intervention groups compared to control or placebo groups. A painful lesson learned from these RCTs is that an RCT should not be initiated in a big population before the detailed biological information on interventions, potential interactions with other environmental chemicals, and probable related metabolic genes has been obtained from pilot and animal studies. Further research on the biological mechanism of interactions between smoking and any other chemicals,

including nutrient supplements and routine drugs for chronic disease prevention and treatment, as well as related metabolic genes is warranted.

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