

Pharmaceuticals

Introduction

Prescription and over-the-counter medications are very widely used in the U.S. and many western countries. A recent study of medication use in the ambulatory adult population of the U.S. revealed that during the previous week, 81 percent of participants had used at least one medication, and half had taken at least one prescription medication. This survey also demonstrated that women aged 65 or older were the highest medication users; specifically, 12 percent of women in this age group took at least 10 different medications and 23 percent took at least five prescription drugs.¹ More recent data from the Slone Survey² indicate that overall and prescription medication use has increased between 1999 and 2005. This study also reinforced earlier estimates that more than 90 percent of women 45 years or older use some medication(s). Further, prescription medication use rates for women 45–64 years old and 65 or older were 68 percent and 82 percent, respectively. Thus, medication use in the U.S. represents a ubiquitous exposure. With breast cancer being the most common cancer in women, a careful evaluation of the potential chemopreventive or carcinogenic effects of common medications is warranted. In this review, we focus on commonly-used medications previously researched in epidemiological studies of breast cancer, including antibiotics, antidepressants, statins, antihypertensives, and non-steroidal anti-inflammatory drugs (NSAIDs).

Exposure Definition and Study Designs

The existing body of literature concerning the use of common medications and breast cancer risk is

largely inconsistent. A primary reason for the divergent findings likely relates to the vast differences in methodologies employed in these studies. In addition to the obvious differences, such as study design (cohort studies vs. case-control studies) previous studies vary greatly with respect to exposure assessment, exposure classification, and adjustment for potential confounding variables. For instance, with respect to exposure assessment, many studies focused on NSAID use and breast cancer risk have only measured aspirin exposure, but have no data on more-recently-used NSAIDs, such as ibuprofen or selective COX-2 inhibitors. Thus, it is possible that women who do not report aspirin use, but are in fact frequent ibuprofen users, might be erroneously classified as “non-NSAID users” because use of these newer drugs was not assessed in some studies.

Further, using the existing research on antibiotic use and breast cancer risk as an example, there are great differences in exposure assessment. Some studies classify antibiotic use as crudely as “ever vs. never,” whereas others have detailed information based on prescription data. Results from cohort studies might be difficult to interpret, as many studies rely on a single measurement of medication use, which does not take into account that medication use is subject to change over time. Many studies of medication use and breast cancer utilize large general practice databases, which improves exposure assessment, but does not allow for adjustment for potential confounding variables, as these are generally not available in these data resources.

Finally, the vast majority of previous studies are so-called secondary data analyses, indicating that these studies were not specifically designed to

address the relationship between common medications and breast cancer risk. Rather, medication use was collected as a potential confounder or within the context of a medical history. While it is standard practice in epidemiological research to analyze data for secondary associations, such studies are always methodologically inferior to those that were specifically designed to assess the link between specific medications and risk of breast cancer.

Studies of medications and breast cancer risk are also complicated by the medications containing non-active ingredients that may affect breast cancer. These ingredients can include phthalates (see Section X, Chapter X of this report), dyes and fillers.

Antibiotics and Breast Cancer Risk

Biological Mechanisms. Antibiotics may influence breast cancer risk via two main biological mechanisms: disruption of intestinal microflora and impact on immune and inflammatory function.³ Naturally occurring gut microflora have been shown to play a role in the conversion of phytochemicals derived from the consumption of plant-based food products into biologically-active substances⁴⁻⁶ suggested to be protective against cancer. For example, phytochemicals such as lignans, can be converted by microflora to enterolactone,⁷ which has been correlated with reduced breast cancer risk.^{8,9} Antibiotics could also theoretically decrease breast cancer risk by affecting the ability of microflora to modulate levels of circulating estrogens through deconjugation of bound estrogens in the gut, freeing them for re-absorption and circulation.¹⁰⁻¹³ However, the disruption of the microflora by antibiotics is not uniform, and may vary by dose

and specific drug formulation.¹⁴

Breast cancer risk may also be mediated by the effect of antibiotics on the human immune system and inflammatory response. Numerous specific biological mechanisms have been suggested, but these remain largely speculative.³ Some antibiotics may have an anti-inflammatory effect by limiting the production of cytokines, or a group of several proteins involved in the immune and inflammatory response.¹⁵ Inhibited cytokine production may be important in limiting estrogen synthesis in the peripheral fat,^{16,17} potentially decreasing cancer risk. There is also limited evidence that some antibiotics may increase the production of prostaglandins, or markers of the inflammatory response.³

Summary of Existing Research. The potential role of antibiotic use in breast cancer etiology gained wide public attention after results from a recent large case-control study became available. In this study of 2,266 breast cancer patients and 7,953 controls who were enrolled in a non-profit health plan, Velicer et al.¹⁸ used computerized pharmacy records to assess exposure to antibiotic drugs. Results indicated that compared to women who never used antibiotics, women with the longest durations of antibiotic use had a two-fold increase in breast cancer risk (OR = 2.07; 95% CI = 1.48–2.89). Similar risk estimates were observed when non-users were compared to women with the greatest number of antibiotic prescriptions (OR = 2.31; 95% CI = 1.69–3.15). Results were very similar for pre- and post-menopausal women and risk was increased for all sub-types of antibiotic drugs. These findings, which sparked considerable public concern about antibiotic use, are somewhat similar to those from a Finish cohort study¹⁹ where ever

having used antibiotics was associated with increased risk of breast cancer among premenopausal women (RR = 1.74; 95% CI = 1.13–2.68), but not postmenopausal women (RR = 0.97; 95% CI = 0.59–1.58). Subsequent population-based²⁰ and nested case-control studies²¹⁻²³ did not report strong associations between antibiotic use and breast cancer risk. Most recently, Friedman and colleagues²⁴ conducted a nine-year follow-up study of over two million women enrolled in the Kaiser Permanente Medical Care Program in northern California. They observed a modest breast cancer risk elevation for women with the highest number of days using tetracyclines (RR = 1.23; 95% 1.11–1.36) and an even more attenuated, non-significant estimate for macrolides (RR = 1.16; 95% CI = 0.98–1.36).

Overall, there is little consensus on whether antibiotic use is associated with breast cancer risk. Any definitive conclusion is complicated by the fact that epidemiological studies cannot distinguish between the potential carcinogenic effect of antibiotic drugs and the potential influence on breast cancer development of the underlying conditions for which these drugs have been prescribed.

Antidepressants and Breast Cancer Risk

Biological Mechanisms. There are several biological mechanisms by which antidepressants may play a role in breast cancer development. One frequently cited laboratory study found that the administration of antidepressants resulted in a significant increase in the development of mammary tumors in rodents.²⁵ This positive association may be due to the structural similarities among common antidepressants and

the cell growth regulating compound N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine HCl, or DPPE. Tricyclic and selective serotonin reuptake inhibitor (SSRI) types of antidepressants have been shown to bind to the same intracellular histamine receptors associated with anti-estrogen binding sites as DPPE.²⁵ However, the presumed effect of antidepressants on tumor growth was not replicated in subsequent *in vitro* studies of human breast tumor cell lines.²⁶

The cytochrome P450 enzyme system has been recognized as an important route of endogenous hormone metabolism, potentially affecting estrogen-dependent breast cancers. Myriad antidepressants have been shown to variably inhibit the cytochrome P450 system,²⁷⁻³⁰ increasing the availability of endogenous estrogens, thereby increasing the risk of breast cancer. Antidepressants are also thought to increase levels of prolactin,^{31, 32} itself a suspected breast tumor promoter. Finally, antidepressants may play a role in immune suppression by suppressing lymphocyte proliferation³³⁻³⁵ suggesting an additional route for increased risk.

Summary of Existing Research In a somewhat recent paper, Lawlor et al.³⁶ conducted a systematic review of previous investigations of the association between antidepressant use and breast cancer risk. This review included seven relevant epidemiological studies published until 2002: two prospective cohorts,^{37, 38} two retrospective cohort studies,^{39, 40} and three case-control studies.⁴¹⁻⁴³ None of the case-control studies generated significant associations between antidepressant use and risk. One prospective cohort study³⁷ reported a significant increase in risk with use of any antidepressant at baseline only (RR = 1.75; 95% CI = 1.06–2.88). In contrast, a

significant decrease in risk (OR = 0.50; 95% CI = 0.30–0.80) was found in one retrospective cohort study.⁴⁰ In light of these inconsistent findings, the authors concluded in their review that the current epidemiological evidence does not support an association between antidepressant use and breast cancer.

Eight epidemiological studies have been published subsequent to the review paper by Lawlor.³⁶ Results from two population-based^{44, 45} and one hospital-based⁴⁶ case-control studies did not demonstrate elevated breast cancer risk among antidepressant users. Similarly, two additional studies using general practice⁴⁷ and health care plan⁴⁸ databases did not reveal significant associations with antidepressant use. Further, Fulton-Kehoe et al.⁴⁹ utilized a large health care plan database and reported a modest increase in risk associated with ever having used amitriptyline (OR = 1.27, 95% CI = 1.10–1.47). However, no dose-response relationship was noted when number of prescriptions were considered, nor were breast cancer risk elevations observed for tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). Finally, Chien et al.⁵⁰ reported results from a recent population-based case-control study where they observed significantly higher risk of progesterone receptor negative (OR = 1.8; 95 % CI = 1.1–3.6) and estrogen receptor positive/ progesterone receptor negative (OR = 2.0; 95% CI = 1.1–3.8) breast cancer among those who had ever used SSRIs compared to those who never used them.

Overall, these additional reports also do not provide strong evidence that would implicate antidepressant use in the etiology of breast cancer. More detailed analyses by tumor hormone receptor status in existing data sets might be

warranted.

Statin Drugs and Breast Cancer Risk

Biological Mechanisms. There is considerable interest and controversy around whether statins may play a role in carcinogenesis. An early laboratory study suggested that these lipid-lowering drugs cause cancer in rodents at amounts that would be comparable to clinically-effective doses in humans.⁵¹ However, several studies published subsequently have called those findings into question. The best-studied route of action for statins appears to be their inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, a key enzyme in the mevalonate pathway of cholesterol synthesis. Inhibition of HMG-CoA reductase inhibits prenylation, a protein synthesis process that leads to cell signaling processes involved in cell proliferation.^{52, 53} Preclinical studies have showed that a variety of statins working through disruption of the mevalonate pathway decrease cell proliferation by promotion of G1 cell cycle arrest and apoptosis in breast cancer cell lines.⁵⁴⁻⁵⁷ Statins have also been shown to decrease mammary tumor formation and metastasis in a mouse model.⁵⁸

Interest in the mevalonate synthesis as target for cancer therapies has grown with the observation that statins may show a synergistic effect with chemoradiation,⁵⁹ chemotherapies,⁶⁰⁻⁶² and COX-2 inhibitors.⁶³ Independent of the mevalonate pathway, statins have been suggested to have anti-cancer properties through an anti-inflammatory effect and via inhibition of the proteasome.⁵²

Summary of the Existing Evidence The association between statin use and breast cancer

risk has been the subject in recent attention in the field of pharmaco-epidemiology. Many of these studies utilized prescription or health care plan record databases. Results from these investigations have consistently not revealed strong associations between statin use and risk.⁶⁴⁻⁷¹ While findings from these geographically-diverse investigations are consistent, they may have to be cautiously interpreted, due to significant methodological shortcomings such as lack of adjustment for confounders and crude exposure assessment (ever vs. never) in many of these studies. Coogan and colleagues⁷² reported findings from a hospital-based case-control study in which prolonged statin use was associated with a two-fold increase in breast cancer risk (OR = 2.1; 95% CI = 1.1–4.0). However, more detailed analyses revealed that this estimate was largely driven by women with in situ disease (OR = 3.4; 95% CI = 1.5–8.0) rather than women with invasive breast cancer (OR = 1.5; 95% CI = 0.7–3.1). Results from a recent population-based case-control study did not demonstrate an increased risk of breast cancer for women who used statin drugs.⁷³ Further, analyses from two large cohort studies, the Nurses Health Study⁷⁴ and the Women's Health Initiative Observational Study⁷⁵ did not reveal significant associations. In contrast, Cauley et al.⁷⁶ described results from a smaller cohort study where ever having used statin drugs was associated with a significant risk reduction (OR = 0.28; 95% CI = 0.09–0.86). However, this estimate was based on only six statin-exposed breast cancer patients and results should be interpreted cautiously. Finally, two recent meta-analyses on this topic did not provide evidence that statin use is linked to breast cancer risk. Thus, considering this diverse and largely consistent body of

evidence, it is unlikely that statin drug use is an important factor in breast cancer development.

Antihypertensive Medications and Breast Cancer Risk

Biological Mechanisms Research into the biological mechanisms by which antihypertensive agents may affect carcinogenesis has focused on calcium channel blockers (CCBs) and Angiotensin-II-converting enzyme inhibitors (ACEis). Pahor has suggested that CCBs could play a role in increased cancer risk,⁷⁷ due to inhibition of apoptosis resulting from diminished intracellular calcium ion concentrations.⁷⁸⁻⁸⁰ However, as reviewed by Mason,⁸¹ the role of calcium ions in apoptosis has been shown to be inconsistent, with intracellular calcium levels yielding both increased and decreased apoptosis across a range of cell types. Additionally, research has shown that CCBs may actually inhibit carcinogenesis by limiting cell proliferation in breast cell lines,^{82, 83} making it difficult to draw firm conclusions about their ultimate effect on cancer risk.

ACEis have been suggested to offer a potential protective effect against cancer risk through the inhibition of angiogenesis. More specifically, ACEis target the action of angiotensin II, part of the rennin-angiotensin system involved with renal blood flow, fluid homeostasis, and blood pressure control.⁸⁴ Angiotensin II has also been shown to promote neovascularization,⁸⁵ a necessary process for tumor development. Early studies showed that angiogenesis and tumor growth were slowed following administration of ACEis in preclinical studies.^{86, 87} Later, Yoshiji and colleagues⁸⁸ hypothesized that the inhibition of angiotensin II inhibits the action of vascular endothelial growth

factor (VEGF), a key enzyme in the angiogenesis process. Although cell proliferation has not been shown to be directly affected,⁸⁹ use of ACEis alone or in combination with other agents decreased VEGF concentrations and angiogenesis,⁹⁰⁻⁹² and reduced blood vessel formation around tumors.⁸⁹

Summary of Existing Evidence. An increasing number of studies have focused on the potential role of antihypertensive drug use in breast cancer development. These studies have largely focused on CCBs, beta-blockers and ACEis; we will restrict our discussion to these widely studied drugs. As with many pharmaco-epidemiological efforts, most of these prior studies were registry-based and utilized data from prescription plan or health care plan records. The limitations of this approach are outlined above. Nevertheless, results from these studies do not indicate that ever having used, or prolonged use of, CCBs, beta-blockers or ACEis were related to elevated breast cancer risk.⁹³⁻⁹⁹ Similarly, results from a large hospital-based case-control study¹⁰⁰ and the Nurses Health Study cohort¹⁰¹ do not suggest that these drugs are related to breast cancer risk. In contrast, findings from a smaller cohort study¹⁰² have linked ever having used CCBs to a significant increase in risk (OR = 2.57; 95% CI = 1.47–4.49). No risk elevations were observed for use of beta-blockers or ACEis. Finally, Li et al.,¹⁰³ in a large population-based case-control study, observed a significant increase in risk for prolonged use (15 years or longer) of beta blockers (OR = 2.1; 95% CI = 1.2–3.7), but no associations with long term use of CCB and ACEis.

While most studies on this topic generated null findings, the majority of these investigations could only crudely classify participants as ever or never having used these drugs. Further, one study with more sophisticated exposure assessment demonstrated an association between breast cancer and prolonged use of beta blockers.¹⁰³ Thus, future studies employing solid epidemiological designs and sophisticated exposure assessment might be needed to definitively rule out a role of antihypertensive medication use in breast cancer development.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Breast Cancer Risk

Biological Mechanism. NSAIDs—including aspirin, ibuprofen, and naproxen—appear to exert an anti-cancer effect through inhibition of the cyclooxygenase (COX) enzyme system. COX-2, in particular, promotes the synthesis of prostaglandins, such as PGE₂, thought to play an etiologic role in tissue generation and tumorigenesis. Additionally, COX-2 has been found to be over-expressed in human breast tumors in multiple studies.¹⁰⁴⁻¹⁰⁶ Preclinical research has shown that the administration of NSAIDs inhibits production of COX enzymes with resulting reduction in tumor progression.¹⁰⁷⁻¹⁰⁹ Moreover, it has been suggested that NSAIDs reduce neovascularization and promote apoptosis.^{110, 111} Some NSAIDs that do not effect the COX system have been shown to induce cell cycle arrest and apoptosis in breast cancer cell lines.¹¹² Taken together, multiple lines of research into the biological mechanisms by which NSAIDs impact cancer risk point to a potentially valid agent in chemoprevention.

Summary of Existing Evidence A large and diverse body of literature exists on the potential chemopreventive effect of NSAIDs use on breast cancer development. Exposure assessment, however, differs widely across studies, including the definition of regular use and prolonged use. Nevertheless, results from most studies have been remarkably consistent. Two registry-based studies^{113, 114} showed significant breast cancer risk reductions for prolonged aspirin use. Several hospital-based studies¹¹⁵⁻¹¹⁷ and population-based studies^{118, 119} have generated statistically significant risk reductions for regular and prolonged aspirin use. Less consistent evidence exists for ibuprofen use, which was associated with decreased risk in one investigation,¹¹⁷ but not in others.^{115, 119} Such discrepancy might not be surprising, given that ibuprofen is still a relatively new drug and to date few people will have had significant exposures to this agent. Findings from the WHI observational study indicated that prolonged use (10 years or more) of any NSAIDs or aspirin was associated with statistically significant breast cancer risk reductions (RR = 0.72; 95% CI = 0.56–0.91 and RR = 0.79; 95% CI = 0.60–1.03, respectively).¹²⁰ Similarly, findings from the CLUE cohort in Washington county¹²¹ point to a chemoprotective effect of aspirin use in breast cancer etiology (RR = 0.46; 95% CI = 0.22–0.98), but results were not influenced by tumor hormone receptor status or COX-2 genetic polymorphisms.¹²² Further support for a chemopreventive role of aspirin comes from the NHANES I¹²³ and Iowa Women's¹²⁴ cohorts, where current or prolonged (six years or longer) use were associated with significant risk decreases (RR = 0.70; 95% CI = 0.56–0.96 and RR = 0.71; 95% CI = 0.58–0.87, respectively).

In contrast, initial analyses from the Cancer Prevention Study II Nutrition cohort,¹²⁵ as well as results from the California Teachers¹²⁶ and Nurses Health Study¹²⁷ cohorts did not demonstrate associations between use of aspirin or other NSAIDs and breast cancer risk. In fact, in the California Teachers cohort, prolonged use (five years or more) of both aspirin and ibuprofen was associated with significant risk elevations for women with hormone receptor negative tumors (RR = 1.8; 95% CI = 1.2–2.92 and RR = 1.50; 95% CI = 1.1–2.03, respectively). In a recent randomized low dose aspirin (100 mg) chemoprevention trial, with an average of ten years of follow-up, women who were randomized to the aspirin intervention arm were not at lower risk of breast cancer compared to women who received the placebo (RR = 0.98; 95% CI = 0.87–1.09). In response to results from this trial, Jacobs et al.¹²⁸ very recently conducted further analyses in the Cancer Prevention Study cohort and focused on long-term (five years or longer) daily use of adult-strength aspirin preparations (≥ 325 mg). The authors speculated that the lack of a protective effect in the randomized trial may be due to the low dose of aspirin, which may not have been sufficient to produce a chemoprotective effect. Results indicated that daily long-term use was associated with a non-significant risk reduction (RR = 0.83; 95% CI = 0.63–1.10).

The existing body of literature on the associations between various NSAIDs and breast cancer risk is complicated and difficult to interpret. While most studies on this topic have demonstrated statistically significant risk reductions, the majority of these studies were either registry-based or employed a case-control design. The former approach is methodologically limited due

to insufficient adjustment for potential confounders, whereas the latter study design is known to be prone to selection and information bias. Further, evidence from cohort studies is inconsistent, although results from most cohort studies point to a role of aspirin in breast cancer chemoprevention. Most importantly, however, the only randomized trial, considered the gold standard in epidemiological study designs, did not demonstrate a chemoprotective effect of aspirin use. It is possible, as suggested by Jacobs et al.¹²⁸ that higher-dose aspirin preparations may be needed to produce a chemoprotective effect. Additional randomized trials with higher aspirin doses may be needed to resolve this important question. It is also possible that selective COX-2 inhibitors have much stronger chemopreventive properties than aspirin. However, in light of the serious side effects revealed in previous trials with these drugs, the use of these drugs in cancer chemoprevention trial is unethical.

Conclusions and Future Directions

The existing literature on the use of common over-the-counter and prescription medications has not definitely linked any of the drugs covered in this review to either increased or decreased risk of breast cancer. Important contributing factors to this apparent inconsistency are likely the numerous methodological issues, discussed throughout this review, associated with the various study designs employed in these investigations. In summary, there is inconclusive evidence on the association between antibiotic use and breast cancer risk; no strong evidence pointing to a significant role of antidepressant and statin drugs in breast cancer development; somewhat inconclusive evidence on the effect of

antihypertensive drugs; and suggestive evidence implicating aspirin use in the chemoprevention of breast cancer.

Future studies with detailed lifetime medication histories are needed to further clarify these important associations. While methodologically superior to case-control studies, it is unlikely that such an assessment can be accomplished with a cohort study design, where repeated detailed medication measurement would be difficult to achieve. Thus, future case-control studies should consider in their design strategies for obtaining detailed and valid lifetime medication histories, which will likely involve a combination between self-report and prescription and/or health care plan data. Further, in light of the strong and largely consistent findings from epidemiological studies that link prolonged higher-dose aspirin use to reduced risk of breast cancer, an adult-dose (325mg) chemoprevention trial might be warranted. Other medications that have not been subjects of epidemiological studies on their relationship to breast cancer may also warrant further investigation. These include medications that supplement thyroid hormones; anti-seizure medications such as Dilantin; steroidal drugs, including those used to treat asthma and those used and abused by young female athletes; and Ritalin, for its possible impact later in life after use in childhood.

As pointed out above, medication use constitutes a ubiquitous exposure in the U.S. and in many countries worldwide. Given that breast cancer is the most common cancer in the U.S. and elsewhere, it is essential that we increase our understanding of the role of commonly used drugs in the etiology of this disease.

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