Review

Use of Common Medications and Breast Cancer Risk

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Abstract

Prescription and over-the-counter medications are widely used in the United States and many western countries. More than two-thirds of women ages >45 years, who are at greatest risk for breast cancer, take prescription medication. In light of the ubiquitous nature of medication use and the fact that breast cancer remains the most common cancer in women, research on the role of medication use in breast cancer etiology is warranted. We summarize the epidemiologic evidence on the association between breast cancer risk and use of common medications, including antibiotics, antidepressants, statins, antihypertensives, and nonsteroidal anti-inflammatory drugs. Overall, there is little evidence that would implicate the use of antibiotics, antidepressants, statins, and antihypertensives in the etiology of breast cancer. Although several prospective studies and a randomized low-dose aspirin chemoprevention trial have not shown lower risk of breast cancer among aspirin users, most studies that have examined the potential chemoprotective effect of nonsteroidal anti-inflammatory drugs have shown significant risk reductions for regular and prolonged use of these drugs. The existing literature on the role of medication use in breast carcinogenesis is complicated. Interpretation of the evidence is hampered due to major methodologic differences across studies, including exposure assessment, exposure classification, and adjustment for potential confounding variables. These differences largely stem from the fact that the majority of articles on this topic represent secondary data analyses from studies with inadequate information on exposure or confounders. Thus, future epidemiologic studies specifically designed to study these ubiquitous and biologically plausible exposures are warranted. (Cancer Epidemiol Biomarkers Prev 2008;17(7):1564–95)

Introduction

Prescription and over-the-counter medications are very widely used in the United States and many western countries. A recent study of medication use in the ambulatory adult population of the United States revealed that 81% of participants have used at least one medication in the past week and that half of the sample reported to have taken at least one prescription medication. This survey also showed that women ages ≥65 years were the highest medication users; specifically, 12% of women in this age group took at least 10 different medications and 23% took at least 5 prescription drugs (1). More recent data from the Slone Survey (2) indicate that overall and prescription medication use has increased between 1999 and 2005. This study also reinforced earlier estimates that >90% of women ages ≥45 years reported any medication use. Further, prescription medication use for women ages 45 to 64 and ≥65 years was 68% and 82%, respectively. Thus, medication use in the United States represents a ubiquitous exposure. In light of the fact that breast cancer remains the most common cancer in women, a careful evaluation of the potential chemopreventive or carcinogenetic effects of common medications is warranted. In this review, we focus on commonly used medications that have been studied previously in epidemiologic studies of breast cancer. These groups of medications include antibiotics, antidepressants, statins, antihypertensives, and nonsteroidal anti-inflammatory drugs (NSAID).

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 versus case-control studies), these 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 introduced NSAIDs such as ibuprofen or selective cyclooxygenase-2 (COX-2) inhibitors.

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Table 1. Epidemiologic studies of the role of antibiotics use in breast cancer development

Study and country	Years	Design	Cases/controls
Danielson et al. (15) Finland	1973-1991	Cohort study	157 cases in Finnish Mobile Clinic Health Examination Survey identified via Finnish Cancer Registry 9,304 cancer-free cohort members (total cohort 9,461)
Lawlor et al. (14) USA	1993-2001	Population-based case-control study	Cases: 2,266 women enrolled in large health plan with primary invasive breast cancer identified from Surveillance, Epidemiology and End Results Controls: 7,953 disease-free health plan members frequency matched 3:1 on age and sex
Wang et al. (16) Denmark	1994-2003	Registry-based study	Cases: 2,728 incident cases identified via population Hospital Discharge Registry Controls: 27,280 controls from population-based Civil Registration System matched 10:1 to cases
Weiss et al. (18) UK	1995-2001	Registry-based study	Cases: 3,708 cases identified from General Practice Research Database Controls: 20,000 frequency matched cancer-free controls
Kaye and Jick (124) UK	1987-2002	Registry-based study	Cases: 1,268 cases identified from those with 6 y recorded medical history in General Practice Research Database Controls: 6,291 cancer-free controls matched to cases up to 5:1
Didham et al. (125) New Zealand	1998-2002	Registry-based study	Cases: 700 cases(including 5 males) identified from General Practitioner Research Database Controls: 700 cancer-free controls matched 1:1 to cases on age, sex, semesters of available data
Velicer et al. (13) USA	1993-2001	Case only	2,266 women with primary invasive breast cancer enrolled in Group Health Cooperative and identified through Surveillance, Epidemiology and End Results Highest number of days antibiotic use (≥1,001) vs none: 2.07 (1.48-2.89); highest number of prescriptions filled (≥51) vs none: 2.31 (1.69-3.15)

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Table 1. Epidemiologic studies of the role of antibiotics use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Self-report questionnaire	History of use of antibacterial treatment of bacteriuria vs none: 1.31 (0.95-1.81) Women ages <50 y, 1.74 (1.13-2.68);women ages >50 y, 0.97 (0.59-1.58)	Age, region type, education, marital status, body mass index (BMI), parity, smoking, height, alcohol use, and screening positive for bacteriuria	
Self-report questionnaire, health plan database	No appreciable difference by menopausal status; therefore all analyses combined Highest number of prescriptions for antibiotics use (≥1001) vs none: 2.07 (1.48-2.89) Highest number of prescriptions filled (≥51) vs none: 2.31 (1.69-3.15)	Age, length of health plan enrollment	Adjustment for following variables did not appreciably affect risk estimates: age at reference date, education, race, number of annual health-care visits, pharmacy co-pay status, age at menarche, parity, age at firth birth >30 y, BMI, family history of breast cancer, high breast density, hysterectomy, menopausal status, age at menopause ≥50 y, oral contraceptive use, and postmenopausal hormone replacement therapy (HRT) use
Epidemiologic prescription database	Highest number of prescriptions for antibiotics (>10) vs none: 1.00 (0.86-1.15) In women ages <70 y: 1.11 (0.93-1.32)	Full sample: HRT use Women ages <70 y; HRT use, age at first birth, and parity	
General practice database/ electronic medical record	Highest number of days of antibiotic use (≥501) vs none: 1.2 (0.9-1.6) By indication vs none: respiratory infection 0.8 (0.7-1.0), urinary tract infection 0.9 (0.6-1.2), skin infection 1.2 (0.9-1.6), other infection 1.0 (0.8-1.3)	Age, calendar year, BMI, alcohol intake, HRT use, NSAID use, prior benign breast disease, utilization of health services, time under observation	
General practice database/electronic medical record	Highest number of days of use (≥501) vs none: 1.2 (0.6-2.4)	Risk estimates not appreciably changed when adjusted for following covariates: BMI, HRT use, history of benign proliferative breast disease, frequency of mammograms, frequency of visits to general practice	
General practice database/electronic medical record	Ever prescription or any antibiotic vs none: 1.02 (1.0-1.05) Ever penicillin vs none: 1.07 (1.02-1.13) Ever macrolide vs none: 0.90 (0.81-0.99) Ever tetracycline vs none: 1.06 (0.97-1.17)	None	Analysis includes male breast cancers analyzed risk using conditional logistic regression
Insurance plan prescription database and cost/ utilization records, self-reported questionnaire	Antibiotic use ≥101 d vs none was not associated with tumor stage, grade, histology, or ER status Regional/distant vs local stage: 1.30 (0.93-1.81) Grade 4 vs 1: 1.39 (0.47-4.16) ER- vs ER+: 1.17 (0.79-1.75) Lobular vs ductal histology: 1.24 (0.79-1.96)	Age, length of enrollment	All OR >1: authors interpret as possible increase in less favorable tumor characteristics with antibiotic use

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Table 1. Epidemiologic studies of the role of antibiotics use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Friedman et al. (12) USA	1994-2003	Registry-based study	Cohort: 2,130,829 female adult health subscribers Cases: 18,521 women with incident invasive breast cancer

Thus, it is possible that women who do not report aspirin use but are in fact frequent ibuprofen users will 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 versus 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. Further, 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, it should be noted that the vast majority of existing studies represent so-called secondary data analyses, indicating that these various 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 in which exposures or confounders is often absent. Although it is standard practice in epidemiologic 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. Summarized below is the existing body of evidence of the associations between the use of common medications, such as antibiotics, antidepressants, statins, and NSAIDs, and breast cancer risk, preceded by a brief discussion of the biological mechanism by which these medications might influence risk.

Antibiotics and Breast Cancer Risk

Biological Mechanisms. A recent review of the biological mechanisms by which antibiotics may influence breast cancer risk suggests two main pathways: disruption of intestinal microflora and effect 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 substances (4-6) 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 reabsorption and circulation (10-13). However, the disruption of the microflora by antibiotics is not uniform and may vary by dose and specific drug formulation (8).

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 (9). Inhibited cytokine production may be important in limiting estrogen synthesis in the peripheral fat (10, 11), 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 nonprofit health plan, Lawlor et al. (14) were able to use computerized pharmacy records to assess exposure to antibiotic drugs. Results indicated that compared with women who never used antibiotics, women with the longest durations of antibiotic use had a 2-fold increase in breast cancer risk [odds ratio (OR), 2.07; 95% confidence interval (95% CI), 1.48-2.89]. Similar risk estimates were observed when nonusers were compared with women with the greatest number of antibiotic prescriptions (OR, 2.31; 95% CI, 1.69-3.15). Results were very similar for premenopausal

Table 1. Epidemiologic studies of the role of antibiotics use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Insurance plan prescription database, subscriber surveys, medical record review	Any antibiotic use vs never 1.14 (1.10-1.18) Use >1,000 d vs none: 1.17 (0.97-1.42) Use >100 d Tetracyclines: 1.23 (1.11-1.36), tetracyclines (excluding ever used macrolides): 1.14 (0.99-1.31) Macrolides: 1.16 (0.98-1.36), macrolides (excluding ever used tetracycline): 1.18 (0.93-1.49) Penicillin: 1.03 (0.94-1.13)	Hormone use	

and postmenopausal women and risk was increased for all subtypes of antibiotic drugs. These findings, which sparked considerable public concern about antibiotic use, are somewhat similar to those from a Finish cohort study (15) where ever use of antibiotics was associated with increased risk of breast cancer among premenopausal women [relative risk (RR), 1.74; 95% CI, 1.13-2.68] but not postmenopausal women (RR, 0.97; 95% CI, 0.59-1.58). Subsequent population-based (16) and nested case-control studies (17-19) did not report strong associations between antibiotic use and breast cancer risk. Most recently, Friedman et al. (12) conducted a 9-year follow-up study of >2 million women enrolled in the Kaiser Permanente Medical Care Program in northern California. They observed a modest risk elevation for women with the highest number of days using tetracyclines (RR, 1.23; 95% CI, 1.11-1.36) and an even more attenuated, nonsignificant estimate for macrolides (RR, 1.16; 95% CI, 0.98-1.36). Finally, in a case-case study, prolonged antibiotic use was not associated with tumor stage, grade, histology, or hormone receptor status (13).

As outlined in Table 1, there is little consensus on whether antibiotic use is associated with breast cancer risk. Any definitive conclusion is complicated by the fact that epidemiologic studies cannot distinguish between the potential carcinogenic effect of antibiotic drugs and the influence of the underlying conditions for which these drugs have been prescribed on breast cancer development.

Antidepressant Use and Breast Cancer Risk

Biological Mechanisms. There are several tentative 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 (20). 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. Tricyclic and selective serotonin reuptake inhibitors (SSRI) types of antidepressants have been shown to bind to the same intracellular histamine receptors associated with antiestrogen binding sites as *N*,*N*-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine HCl (20). However, the presumed effect of antidepressants on tumor growth was not replicated in subsequent *in vitro* studies of human breast tumor cell lines (21).

The cytochrome *P*450 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 *P*450 system (22-25), increasing the availability of endogenous estrogens, thereby increasing the risk of breast cancer. Antidepressants are also thought to increase levels of prolactin (26, 27), itself a suspected breast tumor promoter. Finally, antidepressants may play a role in immune suppression by suppressing lymphocyte proliferation (28-30), suggesting an additional route for increased risk.

Summary of Existing Research. In a recent article, Lawlor et al. (14) conducted a systematic review of previous investigations aimed at exploring the association between antidepressant use and breast cancer risk. This review included seven relevant epidemiologic studies published until 2002: two prospective cohorts (31, 32), two retrospective cohort studies (15, 16), and three case-control studies (33-35). None of the case-control studies generated significant associations between antidepressant use and risk. One prospective cohort study (17) 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 (15). In light of these inconsistent findings, the authors concluded in their review that the current epidemiologic evidence does not support an association between antidepressant use and breast cancer. A small case-control study, nested within a prescription database, which was not covered by the previous review, did not reveal an association between antidepressant use and risk (18).

Several epidemiologic studies have been published subsequent to the review article by Lawlor et al. (ref. 14; Table 2). Results from two population-based (19, 36) and one hospital-based (37) case-control studies did not show elevated breast cancer risk among antidepressant users. Similarly, two additional studies using general practice (38) and health-care plan (39) databases did not reveal

Table 2. Epidemiologic studies of the role of antidepressants use in breast cancer development

Study and country	Years	Design	Cases/controls
Weiss et al. (18) USA	1988-1994	Registry-based study	Cases: 95 cancer recurrences or 78 second primary cancer cases among adults with past history breast, colon, or melanoma Controls: matched 5:1 on age, sex, original cancer type from a cohort of 1,467 patients
Sharpe et al. (22) Canada	1981-1995	Registry-based study	Cases: 5,882 women with incident invasive breast cancer Controls: 23,517 women matched on age and sampling time
Moorman et al. (19) USA	1996-2000	Population-based case-control study	Cases: 938 cases of invasive breast cancer identified via a rapid case ascertainment system Controls: 771 controls selected from DMV and Health Care Financing Administration
Steingart et al. (36) Canada	1996-1998	Population-based case-control study	Cases: 3,133 female cases identified by the Ontario Cancer Registry Controls: 3,062 population controls matched on age and sex
Gonzalez-Perez and Garcia Rodriguez (38) UK	1995-2001	Registry-based study	Cases: 3,708 cases of invasive breast cancer identified from General Practice Research Database Controls: 20,000 controls frequency matched on age, calendar year
Haque et al. (39) USA	1995-2000	Registry-based study	635 cases identified via Kaiser Permanente Southern California health plan cancer registry files Cohort: 109,004 women health plan members with a history of antidepressant use
Coogan et al. (37) USA	1988-2002	Hospital-based case-control study	Cases: 2,138 cases of primary, invasive breast cancer identified via discharge summaries and pathology reports Controls: 2,858 patients without cancer diagnoses frequency matched to cases on age, study center, and interview year

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Table 2. Epidemiologic studies of the role of antidepressants use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Insurance plan prescription database	Ever antidepressant use vs none and cancer recurrence: 0.97 (0.52-1.78) Ever antidepressant use vs none and second primary tumor: 0.94 (0.50-1.77)		Older study but not listed as reviewed by Lawler et al. Nest case-control design but no information given specifically about controls, only about entire cohort
Epidemiologic prescription database	Highest daily dose tricyclic antidepressant vs no use after 11-15 y: 2.02 (1.34-3.04) Genotoxic tricyclic antidepressants: 2.47 (1.37-4.40), nongenotoxic tricyclic antidepressants: 0.99 (0.49-1.99) Highest duration of use (71-100% of 11-15 y) Genotoxic tricyclic antidepressants: 2.39 (1.30-4.39), nongenotoxic tricyclic antidepressants: 1.02 (0.56-1.86)	Age, index date, tricyclic antidepressant use in other periods	Genotoxic tricyclic antidepressants: amoxapine, clomipramine, desipramine, doxepin, imipramine, trimipramine Nongenotoxic tricyclic antidepressants: amitryptyline, maprotiline, nortryptyline, protryptyline
In-person interviews	Any antidepressant use vs none: 1.0 (0.7-1.2) Any antidepressant ≥60 mo vs none: 1.0 (0.5-1.7) Tricyclic antidepressants ≥36 mo vs none: 0.7 (0.3-1.7) SSRI ≥36 mo vs none: 2.2 (0.8-6.3)	Age and race	Adjustment for following variables did not appreciably effect risk estimates: age at menarche, menopausal status, family history of breast cancer in a first-degree relative, oral contraceptive use, HRT use, educational level, BMI, waist-to-hip ratio, alcohol consumption, and cigarette smoking
Self-administered questionnaire	Any regular antidepressant use vs none: 1.17 (1.01-1.36) Highest duration of antidepressant use (≥9 y) vs none: 1.15 (0.78-1.69) Any SSRI use vs none: 1.33 (1.07-1.66) Sertraline: 1.58 (1.03-2.41) Paroxetine: 1.55 (1.00-2.40) Fluoxetine: 1.09 (0.81-1.49) Any tricyclic antidepressant use vs none: 1.12 (0.91-1.37) Amitriptyline: 1.10 (0.85-1.42) Imipramine: 0.88 (0.51-1.51) Doxepin: 1.21 (0.70-2.10) Any MAO-I use vs none: 0.87 (0.35-2.14)	Age	Adjustment for following variables did not appreciably effect risk estimates: height, BMI, age at menarche, parity, age at menopause, oral contraceptive use, alcohol consumption, family history of breast cancer, and history of benign breast disease, clinical depression, or anxiety
General practice database/electronic medical record	Past SSRI use vs none: 0.81 (0.67-1.00) SSRI duration >3 y vs none: 0.56 (0.27-1.18) SSRI high dose vs none: 0.95 (0.46-1.96) Past tricyclic antidepressant use vs none: 0.92 (0.80-1.05) Tricyclic antidepressant duration >3 y vs none: 0.83 (0.62-1.09) Tricyclic antidepressant high dose vs none: 1.11 (0.71-1.71)	Age, calendar year, BMI, alcohol consumption, prior benign breast disease, depression, NSAID use, and HRT use	
Large health plan database/electronic medical record	Ever used paroxetine vs never: 1.12 (0.96-1.31) Used paroxetine ≥2 y vs never: 0.90 (0.66-1.23)	Age	Entire cohort use antidepressants, so controls were users of other medications
In-person interviews	Regular SSRI use vs none: 1.1 (0.8-1.7) Paroxetine vs none: 0.8 (0.3-2.3) Regular SSRI duration ≥4 y vs none: 0.7 (0.4-1.5) Fluoxetine duration ≥4 y vs none: 0.9 (0.4-2.2) Sertraline duration ≥4 y vs none: 1.0 (0.3-4.1)	Age, study center, year of interview, alcohol consumption, religion, family history of breast cancer, and race	

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Table 2. Epidemiologic studies of the role of antidepressants use in breast cancer development (Con't)

Study and country	Years	Design	Cases/controls
Fulton-Kehoe et al. (23) USA	1990-2001	Population-based case-control study	Cases: 2,904 cases of primary invasive or in situ breast cancer in women enrolled in a large HMO, identified via Surveillance, Epidemiology and End Results Controls: 14,396 disease-free controls matched 5:1 to cases on age, calendar year, and length of HMO membership
Lokugamage et al. (24) UK	1946-2005	Cohort	Cohort of 2,253 women followed from birth Cases: 83 women with incident breast cancer
Chien et al. (25) USA	1997-1999	Population-based case-control study	Cases: 975 women age 65-79 y with primary invasive cancer Controls: 1,007 women matched on age, year, and county of residence

significant associations with antidepressant use. In contrast, a large case-control study using the Saskatchewan Prescription Drug Plan (22) showed significant risk elevations for women who were prolonged users of certain genotoxic tricyclic antidepressants (amoxapine, clomipramime, and doxepin; OR, 2.39; 95% CI, 1.30-4.39) but not for nongenotoxic antidepressants (amitriptyline, maprotiline, and nortriptyline; OR, 1.02; 95% CI, 0.56-1.86). Genotoxicity assays were carried out using *Drosophila melanogaster*. Further, Fulton-Kehoe et al. (23) used a large health-care plan database and reported a modest increase in risk associated with ever use of amitriptyline (OR, 1.27; 95% CI, 1.10-1.47). However, no dose-response relationship was noted when number of prescriptions was considered, nor were risk elevations observed for tricyclic antidepressants or SSRI. Results from a small British cohort study did not reveal risk elevations for women who reported antidepressant use at ages 31 or 36 years (24). Finally, Chien et al. (25) reported results from a recent population-based case-control study where they observed significant risk increases for women with progesterone receptor (PgR)–negative tumors (OR, 1.8; 95% CI, 1.1-3.6) and estrogen receptor (ER)–positive/PgR-negative tumors (OR, 2.0; 95% CI, 1.1-3.8).

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 hormone receptor status in existing data sets might be warranted.

Statin Drug Use 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 lipid-lowering drugs cause cancer in rodents at amounts that would be comparable with clinically effective doses in humans (40). 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 reductase, a key enzyme in the mevalonate pathway of cholesterol synthesis. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A reductase thereby inhibits prenylation, a protein synthesis process that leads to cell signaling processes involved in cell proliferation (28, 41). Preclinical studies have shown that a variety of statins working through disruption of the mevalonate pathway decrease cell proliferation by

Table 2. Epidemiologic studies of the role of antidepressants use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Health plan prescription database, self-administered questionnaire	Ever use antidepressants vs never: 1.04 (0.94-1.16) Any antidepressant, 51+ Rx: 1.12 (0.89-1.41) Ever tricyclic antidepressant vs none: 1.06 (0.94-1.19) Ever amitriptyline: 1.21 (1.03-1.41) Ever doxepine: 0.95 (0.79-1.13) Ever imipramine: 1.04 (0.84-1.29) Ever SSRI vs none: 0.98 (0.80-1.18) Any SSRI + Rx: 1.04 (0.73-1.48) Ever fluoxetine: 1.00 (0.80-1.25) Ever paroxetine: 1.00 (0.70-1.41) Ever sertraline: 1.16 (0.81-1.66)	Age, length of enrollment, calendar year, family history of breast cancer, parity/age at first birth, duration of HRT use, BMI, history of screening mammogram in 2 y before reference date	
In-person interviews	Use of an antidepressant at age 31 or 36 vs never use: 0.75 (0.27-2.05)	None	
In-person interview	Ever antidepressant use vs never: 1.2 (0.9-1.6) Antidepressant use among +FHx: 0.4 (0.2-0.9), antidepressant use among -FHx: 1.5 (1.1-2.0) Antidepressant use among ER+: 1.2 (0.9-1.6), antidepressant use among ER-: 1.6 (1.0-2.8) Antidepressant use among PgR+: 1.1 (0.8-1.5), antidepressant use among PgR-: 1.7 (1.1-2.5) Ever tricyclic antidepressant use vs none: 1.2 (0.8-1.8), ever tricyclic antidepressant among +FHx: 0.5 (0.2-1.3), ever tricyclic antidepressant among -FHx: 1.5 (0.9-2.3) Ever SSRI use vs none: 1.2 (0.8-1.8), ever SSRI among +FHx: 0.4 (0.2-1.0), ever SSRI among -FHx: 1.4 (0.9-2.2)	Age, year, county of residence	Adjustment for following variables did not appreciably effect risk estimates: race, income, marital status, education, time since last medical checkup, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of contraceptive use, menopausal hormone use, family history of breast cancer, tobacco smoking, alcohol consumption, BMI, and various medical conditions

promotion of G_1 cell cycle arrest and apoptosis in breast cancer cell lines (29-31, 42). Statins have also been shown to decrease mammary tumor formation and metastasis in a mouse model (32).

Interest in the mevalonate synthesis as target for cancer therapies has grown with the observation that statins may show a synergistic effect with chemoradiation (43), chemotherapies (33, 34, 44), and COX-2 inhibitors (35). Independent of the mevalonate pathway, statins have been suggested to have anticancer properties through an anti-inflammatory effect and via inhibition of the proteasome (41).

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 pharmacoepidemiology (Table 3). Many of these studies used prescription or health-care plan record databases. Results from these investigations have consistently not revealed strong associations between statin use and risk (45-53). Although findings from these geographically diverse investigations are consistent, they may have to be cautiously interpreted due to significant methodologic shortcomings such as lack of adjustment for confounders and crude exposure assessment (ever versus never) in many of these studies. Coogan et al. (54) reported findings from a hospital-based case-control study in which prolonged statin use was associated with 2-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 by women with invasive breast cancer (OR, 1.5; 95% CI, 0.7-3.1). In a more recent report by these investigators, prolonged statin use was not significantly associated with breast cancer risk (55). These latter findings are consistent with those of a population-based case-control study where ever and prolonged statin use was not associated with excess risk (56). Further, analyses from two large cohort studies, the Nurses' Health Study (57) and the Women's Health Initiative Observational Study (58), did not reveal significant associations. In contrast, Cauley et al. (59) described results from a smaller cohort study where ever use of statin drugs was associated with a significant risk reduction (OR, 0.28; 95% CI, 0.09-0.86). However, this estimate was based on a very small number of exposed breast cancer patients ($n = 6$) and results should be interpreted cautiously. Finally, two recent meta-analyses on this topic did not provide evidence that statin use is

Table 3. Epidemiologic studies of the role of statin drug use in breast cancer development

Study and country	Years	Design	Cases/controls
Peeters et al. (52) Denmark	1991-1994	Registry-based study	6 cases were identified using a population-based prescription database and the Danish Cancer Registry 1,882 patients in cohort, with 4,580 person-years of follow-up
Jick et al. (46) Quebec	1988-1994	Registry-based study	Cases: 56 breast cancer cases were identified using computerized health databases of the Regie de l'Assurance-Maladie du Quebec Controls: 560 cancer-free controls matched to cases (6,721 patients in cohort)
Michels et al. (51) UK	1992-1998	Registry-based study	Cases: 224 incident invasive and *in situ* carcinomas from the General Practice Research Database Controls: 1,009 cancer-free matched controls
Li et al. (80) USA	1987-2001	Hospital-based case-control study	Cases: 1,132 primary invasive and *in situ* breast cancer confirmed by pathology report Controls: 589 women with noncancer, non-statin-related conditions
Alshafie et al. (87) USA	1992-2001	Cohort study	244 incident breast cancer cases confirmed by medical record and pathology report 7,284 cancer-free cohort members
Gonzalez-Perez et al. (45) Canada	1989-1997	Registry-based study	879 incidence breast cancers identified through regional cancer registry Cancer-free cohort members (total cohort = 67,472)
Boudreau et al. (56) USA	1997-1999	Population-based case-control study	Cases: 975 primary, invasive cancers identified via tumor registry/Surveillance, Epidemiology and End Results Controls: 1,007 cancer-free general population controls identified via Medicare/Medicaid lists
Kaye and Jick (126) UK	1990-2002	Registry-based study	Cases: 3,224 incident cancer cases, including 698 breast cancers from the General Practice Research Database Controls: 14,844 cancer-free matched controls
Graaf et al. (127) The Netherlands	1991-1998	Registry-based study	Cases: 3,129 incident cancer cases, including 467 breast cancers from the PHARMO drug dispensing database system Controls: 16,976 cancer-free matched controls
Olsen et al. (48) Denmark	1989-2002	Registry-based study	Cases: 22,512 incident cancer cases, including 3,141 breast cancer cases identified via Central Population Register, Epidemiologic Prescription Database, and Danish Cancer Registry Controls: 334,754 men and women in general population, with 12,251 statin users
Brueggemeier et al. (85) USA	1994-2000	Cohort study	Cases: 3,177 incident cases of breast cancer identified from self-report and medical record review

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Table 3. Epidemiologic studies of the role of statin drug use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Epidemiologic prescription database	Use of statins vs none, standardized incidence ratio: 1.4 (0.5-3.1)		
Computerized health record database	Ever used statin vs use of bile acid binding resins: 0.67 (0.33-1.38)	Age at index date, previous neoplasm, year of cohort entry, use of fibric acid, use of other lipid-reducing agents, and a comorbidity score	
General practice database/electronic medical record	Current statin use vs none: 1.0 (0.6-1.6) Past statin use vs none: 1.3 (0.6-2.8) Statin use >5 y vs none: 1.1 (0.4-3.0)		
In-person interview	For all breast cancers, use of statins ≥3 y vs none: 2.1 (1.1-4.0) For carcinoma in situ, use of statins ≥3 y vs none: 3.4 (1.5-8.0) For invasive breast cancer, use of statins ≥3 y vs none: 1.5 (0.7-3.1)	Age, year of interview, study center, education, number of doctor visits two y before hospitalization, use of conjugated estrogens, HRT use, oral contraceptive use, religion, race, alcohol consumption, and BMI	
Questionnaire and interviews	Ever used statins vs none: 0.28 (0.09-0.86) Ever used nonstatin lipid-lowering drug vs none: 0.37 (0.14-0.99) Ever used any lipid-lowering drug vs none: 0.32 (0.15-0.68)	Age and body weight	Adjustment for following variables did not appreciably effect risk estimates: HRT use, family history of breast cancer, mammography use, height, education, health status, age at menarche, age at first birth, parity, physical activity, and alcohol consumption
Computerized health record database	Ever used statins vs none: 1.09 (0.93-1.28) Age ≤55 y and ever used statins vs none: 0.81 (0.53-1.24) Age >55 y and ever used statins vs none: 1.15 (0.97-1.37) Age >55 and ≥37 y HRT use vs none: 2.04 (1.20-3.46)	None	
In-person interview	Ever used statins vs none: 0.9 (0.7-1.2) Current statin use >5 y vs none: 0.7 (0.4-1.0)	Age, reference year, county of residence, use of antihypertensive medication	
General practice database/electronic medical record, self-administered questionnaire	Current statin use vs none: 0.9 (0.6-1.3)	Not specified for breast model, but considered BMI, smoking status, average general practice visit frequency during follow-up	
Drug dispensing database linked to hospital discharge record	Ever statin use vs none: 1.07 (0.65-1.74)	Diabetes mellitus, prior hospitalizations, chronic disease score, chronic use of diuretics, ACEi, CCB, hormones, NSAID, and other lipid-lowering therapy	
Epidemiologic prescription database	Ever statin use vs none: 1.02 (0.76-1.36)	Age, calendar period, NSAID, HRT, cardiovascular drugs	
Self-administered questionnaire	Current statin use vs none: 0.91 (0.76-1.08) Statin use for <2 y vs none: 0.86 (0.68-1.08), statin use for 2-4 y vs none: 0.99 (0.75-1.31), and statin use for >4 y vs none: 0.93 (0.60-1.44)	Age, age at menarche, parity and age at first birth, height, BMI, first-degree family history of breast cancer, benign breast disease, alcohol consumption, physical activity, menopausal status, age at menopause and HRT use	

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Table 3. Epidemiologic studies of the role of statin drug use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Dale et al. (61) USA	N/A	Meta-analysis	N/A
Bonovas et al. (60) N/A	N/A	Meta-analysis	N/A
Hwang et al. (86) USA	1993-2004	Cohort study	Cases: 4,383 incident cases of self-reported breast cancer confirmed by medical record and pathology review Controls: 156,351 cohort members
Setoguchi et al. (91) USA	1994-2003	Registry-based study	Cohort of 31,723 adults with initiation of statin use (24,439) or glaucoma medication use (7,284) Cases: 268 individuals with primary invasive breast cancer
Boudreau et al. (92) USA	1990-2004	Registry-based study	Cohort of 92,788 women ages 45-89 in a large health plan 2,707 incidence invasive breast cancer cases identified through Surveillance, Epidemiology and End Results
Coogan et al. (55) USA	1991-2005	Hospital-based case-control study	Cases: 1,185 women with incident invasive breast cancer admitted to a participating hospital Controls: 2,081 women admitted to a participating hospital without cancer or disorders related to statin use

linked to breast cancer risk (60, 61). 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 Medication Use and Risk of Breast Cancer

Biological Mechanisms. Research into the biological mechanisms by which antihypertensive agents may affect carcinogenesis has focused on calcium channel blockers (CCB) and angiotensin II–converting enzyme inhibitors (ACEi). Pahor et al. have suggested that CCB could play a role in increased cancer risk (62) due to inhibition of apoptosis resulting from diminished intracellular calcium ion concentrations (63-65). However, as reviewed by Mason et al. (66), 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 CCB may actually inhibit carcinogenesis by limiting cell proliferation in breast cell lines (67, 68), making it difficult to draw firm conclusions about their ultimate effect on cancer risk.

ACEi have been suggested to offer a potential protective effect against cancer risk through the inhibition of angiogenesis. More specifically, ACEi target the action of angiotensin II, part of the rennin-angiotensin system involved with renal blood flow, fluid homeostasis, and blood pressure control (69). Angiotensin II has also been shown to promote neovascularization (70), a

Table 3. Epidemiologic studies of the role of statin drug use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Literature database search through July 2005 of randomized clinical trials 27 of 8,943 potential articles were analyzed, representing 86,936 participants	5 studies of breast cancer incidence representing 145 cases Statin use vs none: 1.33 (0.79-2.26)	N/A	
Literature database search through March 2005 of randomized clinical trials or observational studies 16 of 683 potential articles were analyzed	Statin use vs none, in fixed effects model: 1.03 (0.93-1.14) Statin use vs none, in random effects model: 1.02 (0.89-1.18)	N/A	
In-person interview, medical record data	Statin use vs none: 0.91 (0.80-1.05) Hydrophobic statins (Zocor, Mevacor, or Pravachol) vs none: 0.82 (0.70-0.97) Risk did no vary significantly by dose, duration, and HRT use at baseline Tumor characteristics were similar across statin users and nonusers	Age, BMI, race, smoking, family history of breast cancer, education, hysterectomy, mammogram in the last 2 y, age at menarche, parity/age at first birth, alcohol use, percentage of calories from fat, physical activity, and NSAID use	
Epidemiologic prescription database	Statin use vs glaucoma medication use: 0.99 (0.74-1.33)	Age, sex, race, Charlson comorbidity score, physician visits, total medications used, hospitalizations, prior nursing home stay, mammography, gynecologic examination, colonoscopy, fecal occult blood testing, osteoporosis drug use, arthritis, diabetes, inflammatory bowel disease, benign breast disease, HRT use, NSAID use, gastroprotective drug use, obesity, tobacco abuse	
Insurance plan prescription database	Statin use ever vs never: 1.07 (0.88-1.29) Duration ≥5 y: 1.27 (0.89-1.81) Ever statin use among ER+: 1.06 (0.85-1.32) Duration ≥5 y among ER+: 1.24 (0.83-1.86) Ever statin use among ER-: 1.28 (0.78-2.08) Duration ≥5 y among ER-: 1.81 (0.75-4.36)	Age, HRT use, diabetes, use of other lipid-lowering drugs, BMI	
In-person interview	Regular statin use vs never use: 1.2 (0.8-1.8) Statin use duration ≥5 y: 1.5 (0.7-3.2)	Age, interview year, study center, BMI, alcohol consumption, race, education, tobacco use, NSAID use, HRT use, oral contraceptive use, menopausal status, parity, age at menarche, family history of breast cancer, religion	

necessary process for tumor development. Early studies showed that angiogenesis and tumor growth were slowed following administration of ACEi in preclinical studies (71, 72). Later, Yoshiji et al. (73) hypothesized that the inhibition of angiotensin II interferes with the action of vascular endothelial growth factor, a key enzyme in the angiogenesis process. Although cell proliferation has not shown to be directly effected (74), use of ACEi alone or in combination with other agents decreased vascular endothelial growth factor concentrations and angiogenesis (75-77) and reduced blood vessel and formation around tumors (74).

Summary of Existing Evidence. An increasing number of studies have focused on the potential role of antihypertensive drug use in breast cancer development (Table 4). These studies have largely focused on CCB, β-blockers, and ACEi, and we will restrict our discussion to these widely studied drugs. As with many pharmacoepidemiologic efforts, most of these prior studies were registry based such as general practice database or electronic medical records and used data from health-care plan records or prescription plan. The limitations of this approach are outlined above. Nevertheless, results from these studies do not indicate that ever or prolonged use of CCB, β-blockers, or ACEi was related to elevated breast cancer risk (45-49, 78, 79). Similarly, results from a large hospital-based case-control study (50), the Nurses' Health Study cohort (51), and a Dutch cohort study (52) do not suggest that these drugs are related to breast cancer risk. In contrast, findings from a smaller cohort

Table 4. Epidemiologic studies of the role of antihypertensive drug use in breast cancer development

Study and country	Years	Design	Cases/controls
Schreinemachers and Everson (110) UK	1995	Registry-based study	Cases: 80 cases of invasive breast cancer identified from General Practice Research Database Controls: 1,750 total cancer-free controls frequency matched by age and practice location
Egan et al. (117) USA	1989-1996	Cohort study	75 primary invasive cases confirmed by medical record abstraction 3,123 cancer-free cohort members
Olsen et al. (48) Denmark	1991-1993	Registry-based study	32 primary invasive cases identified by population-based Epidemiologic Prescription Database and confirmed via Danish Cancer Registry 17,911 patients in cohort, including men and women (32,540 person-years of follow-up)
Peeters et al. (52) The Netherlands	1974-1985	Cohort	Cohort of 11,075 women ages 50-65 y enrolled in a breast cancer screening project 114 cases of breast cancer identified
Jacobs et al. (115) USA	1988-1994	Cohort study	355 self-reported cancers confirmed by medical record abstraction 18,635 cohort members in analysis (107,256 person-years of follow-up)
Ready et al. (114) USA	1983-1996	Hospital-based case-control study	Cases: 2,893 primary breast cancer cases confirmed from discharge summaries and pathology reports Controls: 6,492 controls admitted for nonmalignant conditions
Harris et al. (113) Denmark	1989-1995	Registry-based study	84 primary invasive cases identified by population-based Epidemiologic Prescription Database and confirmed via Danish Cancer Registry 23,167 cohort members, including men and women (73,193 person-years follow-up)
Johnson et al. (111) UK	1992-1997	Registry-based study	Cases: 3,706 cases of invasive breast cancer identified from General Practice Research Database Controls: 14,155 cancer-free controls from cohort matched 4:1 to cases on age, physician practice, index date, number of years of medical history record in database
Gallicchio et al. (107) Denmark	1989-1995	Registry-based study	83 primary invasive cases identified by population-based Epidemiologic Prescription Database and confirmed via Danish Cancer Registry 17,897 cohort members, including men and women (66,827 person-years follow-up)

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Table 4. Epidemiologic studies of the role of antihypertensive drug use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
General practice database/electronic medical record, self-administered questionnaire	Ever used CCB vs β-blocker users: 1.32 (0.72-2.41)	Smoking, BMI, change of medication, duration of hypertension, diuretic use	
Standardized questionnaire	Ever used CCB vs none: 2.57 (1.47-4.49) Ever used β-blocker vs none: 1.14 (0.58-2.25) Ever used ACEi vs none: 0.93 (0.37-2.34) Ever used any diuretic vs none: 1.38 (0.83-2.29) Ever used any vasodilator vs none: 0.30 (0.07-1.21)	Age, race, parity, age at menopause, self-reported diabetes	
Epidemiologic prescription database	Ever used CCB: standardized incidence ratio: 0.8 (0.5-1.1)	None	
Self-administered questionnaires	No increased in mortality from breast cancer for use of any antihypertensive drug (data not shown)		
Self-administered questionnaire	Use of CCB vs none: 1.07 (0.78-1.48)	Age, multiple drug use, self-reported weight, height, smoking status and mean number of cigarettes smoked per day among women who smoked in 1988, alcohol intake in 1988, physical activity, menopausal status in 1988, postmenopausal HRT use, cholesterol level, systolic and diastolic blood pressure in 1988, aspirin intake, diabetes, history of stroke, myocardial infarction, CABG/PTCA, angina, hypertension in or before 1988, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, age at menopause	
In-person interview	Use of CCB ≥5 y vs none: 1.1 (0.7-1.8) Use of β-blockers ≥5 y vs none: 1.1 (0.9-1.5) Use of ACEi ≥5 y vs none: 1.2 (0.7-2.2)	Age, study center, interview year, BMI, annual visits to physician before diagnosis, race, years of education, breast cancer in mother or sister, benign breast disease, age at menarche, age at first birth, parity, age at menopause, alcohol consumption, duration of oral contraceptive use, duration of HRT use	
Epidemiologic prescription database	Ever used CCB: standardized incidence ratio: 0.97 (0.77-1.20)	None	
General practice database/electronic medical record	ACEi use ≥5 y vs none: 1.0 (0.7-1.5) CCB use ≥5 y vs none: 0.9 (0.7-1.2) β-blocker use ≥5 y vs none: 1.0 (0.8-1.2)	BMI, smoking status	Adjustment for following variables did not appreciably effect risk estimates: alcoholism, hysterectomy, and breast lumps
Epidemiologic prescription database	Ever used ACEi (with previous use of CCB and/or β-blocker): standardized incidence ratio: 1.1 (0.9-1.3) Exclusive ACEi use: standardized incidence ratio: 1.1 (0.8-1.5)	None	

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Table 4. Epidemiologic studies of the role of antihypertensive drug use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Shen et al. (109) UK	1995-2001	Registry-based study	Cases: 3,708 cases of invasive breast cancer identified from General Practice Research Database Controls: 20,000 cancer-free controls from cohort matched to cases on age and calendar year (study cohort = 734,899 women)
Friis et al. (82) USA	1997-1999	Population-based case-control study	Cases: 975 cases of invasive breast cancer identified via Cancer Surveillance System, a population-based cancer registry Controls: 1,007 cancer-free controls identified from list of Medicare/Medicaid recipients, selected for similar age
Moorman et al. (108) Denmark	1990-2002	Registry-based study	264 primary invasive cases identified by population-based Epidemiologic Prescription Database and confirmed via Danish Cancer Registry 49,950 women in total cohort (19,284 statin users contributing 109,985 person-years of follow-up)
Largent et al. (81) USA	1994-1995	Population-based case-control study	Cases: 523 women age 50-75 y with incident breast cancer Controls: 131 women ages 50-75 y old identified through random-digit dialing, matched to cases on age

study (53) have linked ever use of CCB to a significant increase in risk (OR, 2.57; 95% CI, 1.47-4.49). No risk elevations were observed for use of β-blockers and ACEi. Li et al. (80), in a large population-based case-control study, observed a significant increase in risk for prolonged use (≥15 years) of β-blockers (OR, 2.1; 95% CI, 1.2-3.7) but no associations with long-term use of CCB and ACEi. Finally, Largent et al. (81) recently reported results from another population-based case-control study. Results indicated that ever (OR, 1.79; 95% CI, 1.07-3.01) and prolonged (OR, 3.50; 95% CI, 1.64-7.50) use of diuretics was associated with excess risk. No such risk elevations were observed for nondiuretic antihypertensive medications.

Although most studies on this topic generated null findings, the majority of these investigations could only crudely classify participants as ever or never users of these drugs. Further, one study with more sophisticated exposure assessment showed an association between prolonged use of β-blockers (82). Thus, future studies employing solid epidemiologic designs and sophisticated exposure assessment might be needed to definitively rule out the role of antihypertensive medication use in breast cancer development.

NSAID Use and Breast Cancer Risk

Biological Mechanism. NSAIDs, including aspirin, ibuprofen, and naproxen, appear to exert an anticancer effect through inhibition of the COX enzyme system. COX-2, in particular, promotes the synthesis of prostaglandins, such as prostaglandin E_2, thought to play an etiologic role in tissue generation and tumorigenesis. COX-2-derived prostaglandin E_2 may stimulate estrogen biosynthesis in breast tissue (83). Additionally, COX-2 has been found to be overexpressed in human breast tumors in multiple studies (84-86). The observation that COX-2 expression is correlated with aromatase

Table 4. Epidemiologic studies of the role of antihypertensive drug use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
General practice database/electronic medical record	Used diuretics >3 y vs none: 1.1 (0.9-1.2) Used β-blockers >3 y vs none: 1.1 (0.9-1.2) Used ACEi >3 y vs none: 0.9 (0.7-1.2) Used CCB >3 y vs none: 1.0 (0.8-1.2) Used α-blockers >3 y vs none: 0.2 (0.2-1.3)	Age, calendar year, hypertension, BMI, alcohol intake, smoking status, HRT use, and prior breast lump and/or breast biopsy	
In person interview	Used CCB for 15 y vs none: 0.6 (0.3-1.3) Used β-blockers for ≥15 y vs none: 2.1 (1.2-3.7) Used ACEi for ≥15 y vs none: 0.8 (0.4-1.6) Used diuretics for ≥15 y vs none: 1.2 (0.8-1.6)	Reference age	Adjustment for following variables did not appreciably effect risk estimates: race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, HRT use, first-degree family history of breast cancer, smoking status, average daily alcohol intake, and BMI
Epidemiologic prescription database	Ever used any antihypertensive vs never: 0.95 (0.81-1.10) Ever used ace inhibitor vs none: 0.99 (0.75-1.31) Ever used angiotensin II agonist vs none: 1.01 (0.67-1.51) Ever used β-blockers vs none: 0.98 (0.79-1.22) Ever used CCB vs none: 0.80 (0.59-1.09) Ever used diuretic vs none: 0.95 (0.8-1.12) Risk estimates not significantly effected by number of prescriptions, years of follow-up, type of diuretic, or type of calcium antagonist	Age, calendar period, HRT use, NSAID use, parity, and age at first birth	
Self-administered questionnaire	Diuretic use ever vs never: 1.79 (1.07-3.01) Diuretic duration ≥6 y vs never: 3.50 (1.64-7.50) Use of nondiuretic antihypertensive drug ever vs never: 1.18 (0.69-2.03) Nondiuretic antihypertensive duration ≥6 y vs never: 1.24 (0.62-2.50)	Age, BMI, diabetes, smoking, alcohol use, menopausal status, family history of breast or ovarian cancer, age at first pregnancy, education	

expression in breast cancer allows one to formulate the hypothesis that COX-2 increases estrogen production via up-regulation of aromatase expression. Preclinical research has shown that the administration of NSAID inhibits production of COX enzymes with resulting reduction in mammary carcinogenesis (87-89). Moreover, NSAIDs have been suggested to reduce neovascularization and promote apoptosis (63, 90). Some NSAIDs that do not affect the COX system have been shown to induce cell cycle arrest and apoptosis in breast cancer cell lines (64). Taken together, multiple lines of research into the biological mechanisms by which NSAIDs affect 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 NSAID use on breast cancer development (Table 5). Exposure assessment, however, differs widely across studies, including the definition of regular and prolonged use. Nevertheless, results from most studies have been remarkably consistent. Three registry-based studies (91-93) showed significant risk reductions for prolonged NSAID use. Several hospital-based (65, 94-97) and population-based (98-102) studies have generated statistically significant risk reductions for regular and prolonged aspirin use, except for a recent one (103). Less consistent evidence exists for ibuprofen use, which was associated with decreased risk in two investigations (104, 133) but not in others (131, 136, 138). Such discrepancy might not be surprising, given that ibuprofen is still a relatively new drug, and to date, few people have had significant exposures to this agent. Findings from the Women's Health Initiative observational study indicated that prolonged use (≥10 years) of any NSAID or aspirin was associated with statistically significant risk reductions (RR, 0.72; 95% CI, 0.56-0.91 and RR, 0.79; 95% CI, 0.60-1.03, respectively; ref. 105). Similarly, findings

Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development

Study and country	Years	Design	Cases/controls
Schreinemachers and Everson (110) USA	1971-1975	Cohort	1,257 cases identified via the National Health and Examination Survey I 11,411 cancer-free cohort members
Harris et al. (95) USA	1988-1992	Hospital-based case-control study	Cases: 744 patients with newly diagnosed breast cancer identified by collaborating hospitals in northeastern United States Controls: 767 patients without cancer diagnoses frequency matched to cases
Egan et al. (117) USA	1980-1992	Cohort	2,414 cases of invasive breast cancer (2,303 confirmed with medical records and 111 cases identified by questionnaire response)
Harris et al. (99) USA	Not noted	Population-based case-control study	Cases: 511 newly diagnosed breast cancer confirmed by pathology report Controls: 1,534 cancer-free women from central OH frequency matched by race and age
Harris et al. (113) USA	1991-1993	Cohort	393 breast cancers have been detected 32,505 women enrolled in the mammography screening program of The Ohio State University Comprehensive Cancer Center (4.7 y average follow-up)
Coogan et al. (65) USA	1976-1996	Hospital-based case-control study	Cases: 6,558 women with a first occurrence of primary breast cancer diagnosed within the previous year, confirmed by path report, and no concurrent or previous cancer Controls: 3,296 patients with other cancers not associated with NSAID use, 2,925 noncancer patients
Sharpe et al. (93) Canada	1981-1995	Registry-based study	Cases: 5,882 women diagnosed with histologically proven invasive breast cancer Controls: 23,517 controls frequency matched on age and sampling time
Khuder and Mutgi (120) N/A	N/A	Meta-analysis	N/A

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
In-person and telephone interviews, hospital and nursing home records	Incident risk ratio for all sites combined for aspirin users vs nonaspirin users (30 d before interview) All sites combined: 0.83 (0.74-0.93), lung cancer: 0.68 (0.49-0.94), breast cancer in women: 0.70 (0.50-0.96), and colorectal cancer in younger men: 0.35 (0.17-0.73)	Gender, age	Adjustment for following variables did not appreciably effect incident risk ratio: race, education, smoking, alcohol
In-person interview	1-4 y NSAID use vs none: 1.09 (0.8-1.5), ≥5 y NSAID use vs none: 0.63 (0.5-0.9)	Age, menopausal status, parity, family history of breast cancer, BMI	
Self-administered questionnaire, medical record review	Regular aspirin use from 1980 to 1988 vs no regular use: 1.01 (0.80-1.27) Heavy use from 1980 to 1988 vs no regular use: 1.09 (0.75-1.60) ≥20 y regular use vs no regular use: 1.00 (0.71-1.41)	Age at menarche, age at menopause, BMI, alcohol, family history of breast cancer, history of benign breast disease, multivitamin use	Authors concluded that regular aspirin use does not reduce breast cancer risk
In-person interview	Regular NSAID use vs no regular use: 0.66 (0.52-0.83) Regular aspirin use vs no regular use: 0.69 (0.46-0.99) Regular ibuprofen use vs no regular use: 0.57 (0.36-0.91) ≥7 per week, ≥5 y NSAID use vs no regular use: 0.60 (0.40-0.91)	Age, parity, menopausal status, family history	
Self-administered questionnaire	1-3 NSAID pills per week vs <1: 0.64 (0.50-0.82), ≥4 vs <1: 0.57 (0.44-0.74)	None	Adjustment for the following variables did not appreciably effect risk estimates: age, education, parity, menopausal status, and family history of breast cancer
In-person interview	For cancer controls: regular use within 1 y of admission only vs never use: 0.6 (0.4-1.0); regular use begun ≥1 y before admission vs never use: 0.8 (0.7-1.0) For noncancer controls: regular use within 1 y of admission only vs never use: 0.5 (0.3-0.8), regular use begun ≥1 y before admission vs never use: 0.7 (0.6-0.9)	Age, study center, interview year, years of education, history of benign breast disease, number of doctor visits 2 y before admission, duration of oral contraceptive use, duration of use of female hormone supplements	Adjustment for the following variables did not appreciably effect risk estimates: age at menarche, age at menopause, age at first birth, parity, race, alcohol consumption, religion, breast cancer in mother or sister, practice of breast self-examination, BMI
Saskatchewan Prescription Drug Plan database	NSAID exposure 2-5 y before diagnosis: average daily dose >0.3 vs ADD = 0: 0.76 (0.63-0.92) Just cases, exposure 2-5 y before diagnosis: $0 < ADD \leq 0.1$ vs ADD = 0: 0.52 (0.37-0.73), $0.1 < ADD \leq 0.3$ vs ADD = 0: 0.53 (0.30-0.92), and ADD > 0.3 vs ADD = 0: 0.49 (0.24-0.99)	Sampling fractions, age, exposure during other periods, total duration of lactation, BMI after menopause	For periods <2 and >5 y, there was no significant reduction in risk
Literature database search through 2000 14 articles were analyzed	NSAID use vs none 0.82 (0.75-0.89) in all studies, 0.78 (0.62-0.99) in 6 cohort studies, and 0.87 (0.84-0.91) in 8 case-control studies	N/A	The numbers given in Table 3 are different than the numbers presented in the body of the article

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Cotterchio et al. (98) Canada	1996-1998	Population-based case-control study	Cases: 3,133 random women diagnosed with a first primary cancer of the breast, 25-74 y identified via Ontario Cancer Registry Controls: 3,062 age-matched random sample of the female population of Ontario
Meier et al. (128) UK		Registry-based study	Cases: 3,706 women with incident breast cancer Controls: 14,155 age, years of medical history in the computer record, general practice attended, and calendar time matched controls
Johnson et al. (111) USA	1986-1997	Cohort	938 cases identified from the Iowa Women's Health Study 27,616 total cohort members
Harris et al. (105) USA	Not noted	Cohort study	1,392 self-reported incident cases confirmed by medical record review 80,741 women in total cohort (43-mo average follow-up)
Moorman et al. (100) USA	1996-2000	Population-based case-control study	Cases: 930 cases of invasive breast cancer identified via North Carolina Central Cancer Registry Controls: 754 controls selected from DMV and Health Care Financing Administration, frequency matched to cases on age and ethnicity
Gonzalez-Perez et al. (122) N/A	N/A	Meta-analysis	N/A
Garcia Rodriguez and Gonzalez-Perez (104) UK	1995-2001	Registry-based study	Cases: 3,708 cases of invasive breast cancer identified from General Practice Research Database Controls: 20,000 cancer-free controls from cohort matched to cases on age and calendar year (study cohort = 734,899 women)
Terry et al. (102) USA	1996-1997	Population-based case-control study	Cases: 1,508 invasive or in situ breast cancer cases confirmed by medical record review Controls: 1,556 controls selected though random-digit dialing methods and Health Care Financing Administration lists, frequency matched to cases in 5-y age intervals

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Self-report questionnaire	Any regular NSAID use vs never: 0.76 (0.66-0.88) ≥9 y NSAID use vs never: 0.68 (0.54-0.86) ≤1 y since last NSAID use vs never: 0.64 (0.54-0.77) Age at first use ≥50 vs never: 0.76 (0.61-0.93)	Age, history of arthritis, benign breast disease	Confounders evaluated include HRT, oral contraceptive use, alcohol, smoking, weight, BMI, physical activity, history of arthritis, reproductive history, education, marital status, previous breast cysts, family history of breast cancer, other medication use, dietary fat intake
Medical history computer record	20-29 acetaminophen prescriptions vs none: 0.7 (0.6-0.9) ≥30 acetaminophen prescriptions vs none: 0.8 (0.7-1.0) No statistically significant difference found between number of NSAID prescriptions	Smoking status, BMI	Adjustment for following variables did not appreciably effect risk estimates: prior hysterectomy, prior oophorectomy, prior history of benign breast lumps, longer-term exposure to postmenopausal estrogens Study contains no information about over-the-counter NSAID
Self-administered questionnaire	Aspirin or NSAID use vs none: 0.80 (0.67-0.95) Aspirin use vs none: 0.82 (0.71-0.95) NSAID use vs none: 0.98 (0.85-1.14) ≥6 aspirin use per week vs none: 0.71 (0.58-0.87) In situ disease: ≥6 aspirin use vs none: 0.52 (0.30, 0.90) Regional or distant disease: ≥6 aspirin use vs none: 0.50 (0.29-0.88)	Age, BMI, estrogen use, family history of breast cancer, benign breast disease, multivitamin use, category of NSAID use, mammography, waist-to-hip ratio	
Self-administered questionnaire	Any NSAID use for ≥10 vs <1 y use: 0.72 (0.56-0.91) Aspirin use for ≥10 vs <1 y use: 0.79 (0.60-1.03) Ibuprofen use for ≥10 vs <1 y use: 0.51 (0.28-0.96)	Age, ethnicity, education, BMI, HRT use, family history of breast cancer, parity at age <30 y, and episodes of weekly exercise	Additional analyses stratified by BMI, HRT use, family history of breast cancer, parous at age <30 y, and episodes per week of moderate/strenuous exercise did not vary appreciably from full sample
In-person interview	Any NSAID use vs none: 0.4 (0.3-0.6) Occasional NSAID use vs none: 0.5 (0.3-0.7) Regular NSAID use ≥3 y vs none: 0.3 (0.2-0.5)	Age, race, age at menarche, age at first full-term pregnancy, breastfeeding history, menopausal status, family history, oral contraceptive use, HRT use, education, BMI, waist-to-hip ratio, smoking status, and offset term	
Literature database search from 1966 to 2002 for cohort or case-control studies 15 of 47 studies reporting outcomes for breast cancer were analyzed	NSAID use vs none: 0.77 (0.66-0.88) Aspirin use vs none: 0.77 (0.69-0.86)	N/A	
General practice database/electronic medical record	Aspirin use ≥4 y vs none: 0.86 (0.61-1.19) Nonaspirin NSAID (ibuprofen) use ≥4 y vs none: 0.94 (0.74-1.21) Acetaminophen use ≥4 y vs none: 0.77 (0.64-0.94)	Age, calendar year, BMI, alcohol intake, smoking status, HRT use, prior benign breast disease, and remaining NSAID	
In-person interviews, medical records	Aspirin use ≥7 times/wk for ≥5 y vs none: 0.77 (0.57-1.04) Ibuprofen use ≥3 times/wk for ≥5 y vs none: 1.09 (0.70-1.70) Ever used aspirin and hormone receptor positive vs none: 0.74 (0.60-0.93) Ever used aspirin and hormone receptor negative vs none: 0.97 (0.67-1.40)	Age at diagnosis, migraine headache, BMI	

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Harris et al. (160) N/A	N/A	Meta-analysis	N/A
Jacobs et al. (115) USA	1992-2001	Cohort study	3008 incident cases identified via self-report and confirmed via medical record or state cancer registries 97,786 women in total cohort
Zhang et al. (97) USA	1976-2002	Hospital-based case-control study	Cases: 7,006 primary breast cancer cases confirmed from discharge summaries and pathology reports Controls: 3,622 controls admitted for nonmalignant conditions
Swede et al. (96) USA	1982-1998	Hospital-based case-control study	Cases: 1,478 primary, incident cases confirmed via pathology report Controls: 3,383 cancer-free controls frequency matched to cases on 5-y age intervals
Marshall et al. (116) USA	1995-2001	Cohort	Cases: 2,391 primary incident cases confirmed by tumor registry 114,640 disease-free cohort women
Rahme et al. (129) Canada	1998-2002	Registry-based study	Cases: 1,090 incident cases identified from mammography screening group Controls: 44,990 disease-free women from mammography screening group (418,458 women in total cohort)
Moorman et al. (108) USA	1993-2001	Population-based case-control study	Cases: 763 cases of invasive or in situ breast cancer among African American women Controls: 678 disease-free African American population controls matched by age

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Literature database search through 1970-2003	All studies NSAID vs no use: RR, 0.61 (0.50-0.75) 17 studies	N/A	
Self-administered questionnaire	≥60 tablets of any NSAID per month vs none: 1.07 (0.96-1.21) ≥60 aspiring tablets per month vs none: 1.01 (0.84-1.20) ≥60 ibuprofen tablets per month vs none: 1.06 (0.89-1.26) ≥5 y current regular NSAID use vs none: 1.05 ((0.88-1.26) ≥5 y current regular aspirin use vs none: 0.88 (0.69-1.12) ≥5 y current regular ibuprofen use vs none: 1.29 (0.92-1.82)	Age, race, education, family history of breast cancer, personal history of breast cysts, history of mammography, age at menarche, duration of oral contraceptive use, parity, age at menopause, HRT use, weight change, BMI, alcohol consumption	
In-person interview	≥20 y regular aspirin use vs none: 0.59 (0.25-1.36) ≥5 y regular ibuprofen use v none: 0.78 (0.29-2.08) Regular use of aspirin and hormone receptor positive vs none: 0.74 (0.44-1.26) Regular use of aspirin and hormone receptor negative vs none: 0.94 (0.45-1.96) Regular use any NSAID and premenopausal vs none: 0.62 (0.41-0.94) Regular use any NSAID and postmenopausal vs none: 0.90 (0.69-1.16)	Age, year of interview, study center, race, year of education, benign breast disease, number of physician visits 2 y before hospitalization, duration of HRT use, duration of oral contraceptive use, age at menarche, age at menopause, age at first birth, parity, alcohol consumption, family history of breast cancer, practice of breast self-exam, and BMI	
Self-administered questionnaire	Regular aspirin use vs none: 0.85 (0.74-0.97) ≥7 aspirin tablets/week vs none: 0.74 (0.59-0.92) ≥10 y aspirin use vs none: 0.91 (0.78-1.06) Daily regular use of aspirin for ≥10 y vs none: 0.72 (0.53-0.97)	Age at menarche, age at first birth, BMI, history of first-degree relative with breast cancer, and history of benign breast disease	
Self-administered questionnaire, cancer registry data	Daily use aspirin vs none: 0.98 (0.86-1.13); ≥5 y regular use vs none: 1.07 (0.96-1.20) Daily use ibuprofen vs none: 1.24 (1.07-1.44); ≥5 y use vs none: 1.17 (1.00-1.36) Daily use any NSAID vs none: 1.09 (0.97-1.21); ≥5 y regular use vs none: 1.11 (1.01-1.23) Daily use acetaminophen vs none: 0.99 (0.74-1.31); ≥5 y vs none: 1.10 (0.95-1.27) ER/PgR negative and aspirin use ≥5 y daily vs none: 1.81 (1.12-2.92); ER/PgR positive and ibuprofen use ≥5 y daily vs none: 1.50 (1.11-2.03)	Race, BMI, first-degree family history, menopausal and hormone therapy use status, smoking, alcohol intake, physical activity, mammography history, breast biopsy history, parity before age 30, neighborhood SES	
Population prescription/ medical record database	COX-2 inhibitors ≥90 d vs none: 0.81 (0.68-0.97) NSAID ≥90 d vs none: 0.65 (0.43-0.99) Aspirin > 100 mg/d for ≥90 d vs none: 0.75 (0.64-0.89) Acetaminophen ≥90 d vs none: 0.91 (0.71-1.16)	Age, mammography in year 2 or 3 before index date, breast procedure in the prior 3 y, benign neoplasm of the breast in prior 3 y, other breast disease in the prior 3 y, HRT in prior year, visit to gynecologist in prior year	
In-person interviews, genotyping by Taqman assay	COX-2 gene wild-type homozygous or heterozygous and regular NSAID use vs none: 0.3 (0.1-0.9) COX-2 gene variant homozygous and regular NSAID use vs none: 0.3 (0.2-0.6)	Age, offset term for oversampling younger and African American women	

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Cook et al. (118) USA	1992-2004	Randomized controlled trial	39,876 women randomized into low-dose aspirin (19,934) and placebo (19,942) arms followed for self-reported cancer endpoints verified by medical record review
Harris et al. (94) USA	2003-2004	Hospital-based case-control study	Cases: 323 cases of histologically confirmed invasive breast cancer Controls: 649 age, race, and residence matched controls from hospital mammography service
Gallicchio et al. (106) USA	1989-2003	Cohort	Cases: 91 cases of invasive or in situ breast cancer identified via county and state cancer registries 1,467 women with benign breast disease identified from larger CLUE II cohort of 14,625 women
Shen et al. (109) USA	1996-1997	Population-based case-control study	Cases: 1,067 in situ or invasive breast cancer cases included in the Long Island Breast Cancer Study Project Controls: 1,110 frequency matched on age identified through random-digit dialing
Gill et al. (153) USA1993-2002	1993-2002	Cohort	1,830 breast cancer cases in the Multiethnic cohort 98,920 women in cohort
Jacobs et al. (119) USA	1992-2003	Cohort	571 breast cancer cases in Cancer Prevention Study II Nutrition cohort 76,303 total women in cohort

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Self-administered questionnaire	Aspirin use vs placebo: 0.98 (0.87-1.09) Marginal interaction between aspirin use and smoking status, P < 0.09 Never smokers: 1.11 (0.94-1.30), former smokers: 0.84 (0.70-1.01), and current smokers: 0.93 (0.69-1.25)	None	
In-person interview	Daily COX-2 inhibitor use ≥2 y vs none/infrequent use: 0.29 (0.14-0.59) Aspirin use 2 times per week for ≥2 y vs none/infrequent use: 0.49 (0.26-0.94) Ibuprofen/naproxen use 2 times per week for ≥2 y vs none/infrequent use: 0.37 (0.18-0.72)	Age, BMI, parity, menopausal status, family history, smoking and alcohol intake	None/infrequent use defined as use of no more than one pill per week for <1 y
Self-report questionnaire, medical record data, and biological sample for COX genotyping via Taqman assay	Aspirin use in 1989 vs none: 0.46 (0.22-0.98) Aspirin use in 1996 vs none: 0.47 (0.18-1.21) Any NSAID use in 1989 vs none: 0.60 (0.35-1.03) Any NSAID use in 1996 vs none: 0.64 (0.32-1.27) No association between COX genotype and breast cancer risk Suggestion of significantly increased risk among those with COX-2 rs2143416 variant CC genotype and nonuse of NSAIDs	Age, type of NSAID	Adjustment for following variables did not appreciably effect risk estimates: education, age at menarche, menopausal status in 1989, alcohol consumption in 1989, family history of breast cancer, BMI in 1989, and parity
In-person interview	No major effects of the three COX-2 variant alleles on breast cancer risk were found Among women with hormone receptor-positive breast cancer, reduced risk for any NSAID use was only evident among those who had at least one variant C allele of COX-2 0.8473 NSAID use vs none: 0.7 (0.5-1.0) P for the interaction = 0.02	Age at reference (defined as age at diagnosis for cases and age at identification for controls)	Variables found not to confound associations of interest: age at menarche, parity, lactation, months of lactation, age at first birth, number of miscarriages, history of fertility problems, alcohol, race, education, religion, marital status
Self-administered questionnaire	No association between breast cancer risk and duration of aspirin use for current or past users vs nonusers was found Duration of current other NSAID use protective vs nonusers (≥6 y): 0.70 (0.51-0.95) When stratified by ethnicity and hormone receptor status, the protective effect limited to Caucasians or African Americans or to women with at least one positive hormone receptor	Age, ethnicity, BMI, family history of breast cancer, education, mammography screening, alcohol intake, age at menarche, age at fist live birth, number of children, menopausal status, and HRT	
Self-administered questionnaire	Less than daily, low-dose, or past use vs no reported use: 1.10 (1.00-1.21) Not statistically significant lower risk for current daily use (≥325 mg) ≥5 y: 0.83 (0.63-1.10)	Age, race, education, smoking, BMI, physical activity level, use of HRT, history of mammography, history of colorectal endoscopy, use of use of nonaspirin NSAIDs, history of heart attack, diabetes, hypertension	Adjustment for following variables did not appreciably effect risk estimates: nutritional factors

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Ready et al. (114) USA	2000-2002	Cohort	482 breast cancer cases in VITAL cohort study 35,323 total postmenopausal women in cohort
Gallicchio et al. (107) USA	1989-2006	Cohort	430 cases of primary invasive breast cancer identified from cancer registries 18,723 total women in cohort
Bardia et al. (112) USA	1992-2003	Cohort	3,487 incident cancer cases and 3,581 deaths were observed in the cohort of 22,507 postmenopausal women
Davis and Mirick (103) USA	1992-1995	Population-based case-control study	Cases: 600 newly diagnosed breast cancer Controls: 647 from the Seattle metropolitan area, identified by random-digit dialing and frequency matched by 5-y age groups
Slattery et al. (101)	1999-2004	Population-based case-control study	Cases: 798 Hispanic/Native American and 1,527 non-Hispanic White women diagnosed with first primary breast cancer Controls: 935 Hispanic/Native American and 1,671 non-Hispanic White women from the target populations matched on ethnicity and 5-year age distribution of cases

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Self-administered questionnaire	Low-dose aspirin overall use vs none: 0.99 (0.80-1.23) Low-dose aspirin at ≥4 d/wk over 10 y vs none: 0.65 (0.43-0.91) All NSAIDs (except for low-dose aspirin) overall use vs none: 0.98 (0.67-1.44) All NSAIDs (except for low-dose aspirin) ≤1-3 d/wk over 10 y vs none: 0.78 (0.61-0.98) All NSAIDs (except for low-dose aspirin) ≥4 d/wk over 10 y vs none: 1.26 (0.96-1.65) Regular/extra-strength aspirin at ≥4 d/wk over 10 y vs none: 1.43 (1.02-2.00)	Age, race, BMI, family history of breast cancer, history of biopsy, mammogram in 2 y before baseline, age at menarche, age at first birth, age at menopause, history of surgical menopause, years of combined estrogen and progesterone hormone therapy, multivitamin use and alcohol use, adjustment for use of other categories of NSAIDs	
In-person interview	Nonaspirin NSAID use in 1996 vs nonusers: 0.53 (0.31-0.93) NSAID use at baseline and in 1996 vs no NSAID use at baseline and in 1996: 0.50 (0.28-0.91)	Age at baseline	Adjustment for following variables did not appreciably affect risk estimates: education, history of fibrocystic disease, family history of breast cancer, age at first menarche, hormone use, oral contraceptive use, menopausal status, parity, BMI
Self-administered questionnaire	Aspirin use vs nonuse was inversely associates with total cancer incidence: 0.84 (0.77-0.90) or cancer mortality: 0.87 (0.76-0.99) The inverse relationship was stronger among former and never smokers vs current smokers Nonaspirin NSAID use was not associated with cancer incidence or mortality	Age, education status, physical activity, use of HRT, marital status, BMI, diabetes status, fruit and vegetable intake, waist-to-hip ratio, history of hypertension, alcohol use, vitamin supplement use, total caloric intake, red meat consumption, whole-wheat consumption, vitamin E intake, cholesterol intake, history of osteoarthritis, and history of rheumatoid arthritis	No information according to sites
Telephone interview	No association between risk of breast cancer and any measure of NSAID use Ever regular NSAID use vs never: 1.1 (0.8-1.4) <5 y vs never: 1.1 (0.7-1.8) 5-10 y vs never: 1.0 (0.7-1.5) ≥2 y before diagnosis vs never: 2.0 (0.9-4.3) <2 y diagnosis vs never: 1.0 (0.7-1.3) Among cases with localized disease, ≥2 y before diagnosis vs never: 2.2 (1.0-4.9)	Parity, age at first pregnancy, mother/sister breast cancer, early double oophorectomy, oral contraceptive use, ever upper gastrointestinal series, and ever smoker (all subjects); mother/sister breast cancer ages <45 y and alcohol intake (if premenopausal) or HRT (if postmenopausal)	
In-person interview	Aspirin use vs nonuse among postmenopausal women with no recent hormone exposure: 0.56 (0.33-0.96) Aspirin use among postmenopausal women with recent hormone exposure or premenopausal/perimenopausal women was not associated with breast cancer risk Interleukin-6 genotype modified the association between aspirin and breast cancer among postmenopausal women with no recent hormone exposure (P for interaction = 0.04 for Hispanic/Native American and 0.06 for non-Hispanic White)	Age, study center, referent year BMI, lifetime physical activity score, parity, and percentage Native American ancestry	

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Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Study and country	Years	Design	Cases/controls
Friis et al. (82) Denmark	1993-2003	Cohort	847 cases identified via the Danish Cancer Registry 29,875 total cohort member
Mangiapane et al. (121) N/A	N/A	Meta-analysis	N/A
Zhang et al. (83) USA	1992-2004	Randomized controlled trial	39,876 women randomized into low-dose aspirin (19,934) and placebo (19,942) arms followed for self-reported cancer endpoints verified by medical record review

from the CLUE cohort in Washington county (106) 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 hormone receptor status or *COX-2* genetic polymorphisms (107). Other studies have also attempted to assess the effect of the *COX-2* gene on the association between NSAID use and breast cancer risk, but results have been inconsistent (108, 109). Further support for a chemopreventive role of aspirin comes from the National Health and Nutrition Examination Survey I cohort (110) and Iowa Women's cohort (111) where current or prolonged (≥6 years) 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 the Iowa Women's cohort, these risk reductions were still apparent in subsequent analyses based on more breast cancer patients (112). These findings are similar to those of a smaller cohort from Ohio (113), where frequent NSAID use was associated with a significant risk reduction (RR, 0.57; 95% CI, 0.44-0.74). Recently, Ready et al. (114) found significant risk reduction for frequent and long-term use of low-dose aspirin (≥4 days/wk over 10 years) in the Vitamins and Lifestyle cohort (RR, 0.65; 95% CI, 0.43-0.91).

In contrast, initial analyses from the Cancer Prevention Study II Nutrition cohort (115) as well as results from the California Teachers (116) and Nurses' Health Study (117) cohorts did not show associations between use of aspirin or other NSAIDs and breast cancer risk. In fact, in the California Teachers cohort, prolonged use (≥5 years) of both aspirin and ibuprofen was associated with significant risk elevations for women with hormone receptor-negative tumors (RR, 1.8; 95% CI, 1.12-2.92 and RR, 1.50; 95% CI, 1.1-2.03, respectively). The Danish Diet, Cancer and Health cohort study (82) also showed increased breast cancer incidence among both any NSAID and aspirin-only users (RR, 1.27; 95% CI, 1.10-1.45 and RR, 1.31; 95% CI, 1.12-1.53, respectively), although this cohort women had higher breast cancer incidence than women in the general Danish population and most chronic aspirin use came from low-dose aspirin. In the Multiethnic cohort [153], authors observed no association between aspirin and breast cancer but found that current other NSAID use was protective among Caucasian and African American as well as among women with at least one positive hormone receptor. In a randomized low-dose aspirin (100 mg) chemoprevention trial (118), with an average of 10 years of follow-up, women who were randomized to the aspirin intervention arm were not at lower risk of breast cancer compared with women who received the placebo (RR, 0.98; 95% CI, 0.87-1.09). In subgroup analyses, low-dose aspirin showed no effects by tumor characteristics at diagnosis (83) but suggested protective effects by smoking status (RR, 0.84; 95% CI, 0.70-1.01; ref. 118). Consistently, the Iowa Women's Health Study showed that the inverse association between total cancer incidence (and mortality) and aspirin use was stronger among former and never smokers than current smokers (112). However, results from the Women's Health Study, a randomized prevention trial, did not reveal lower risk of breast cancer in the treatment group after an average of 10 years of follow-up of almost 40,000 women (83, 118). It should be noted, though, that low-dose aspirin (100 mg every other day) was administered in this trial. Jacobs et al. (119) conducted further analyses in the Cancer Prevention Study II Nutrition cohort and focused on long-term (≥5 years) daily use of adult-strength aspirin preparations (≥325 mg). The authors speculated that the lack of a protective effect in the randomized trial might be due to the administration of low-dose aspirin tablets, which may not have been sufficient to produce a chemoprotective effect. Results indicated that daily long-term use was associated with a nonsignificant risk reduction (RR, 0.83; 95% CI, 0.63-1.10).

Finally, four meta-analyses showed significant chemopreventive effects of aspirin or NSAIDs against breast cancer. The first considered 14 studies published until 2000 (120) and showed a significant risk reduction associated with NSAID use (OR, 0.82; 95% CI, 0.75-0.89). A more recent meta-analysis restricted to 10 epidemiologic studies published from 2001 to 2005 (121) supported a protective association between aspirin intake and breast cancer (RR, 0.74; 95% CI, 0.69-0.79) with

Table 5. Epidemiologic studies of the role of NSAID use in breast cancer development (Cont'd)

Exposure measurement	Major findings	Confounders	Comments
Self-administered questionnaire at baseline (1993-1997) and data updated using a nationwide prescription database through 2-3	Any NSAID use at baseline vs nonuse: 1.27 (1.10-1.45) Similar results were observed in a combined analysis of baseline and prescription data Aspirin only use vs nonuse: 1.31 (1.12-1.53) No differences in risk estimates with frequency, recency, or duration of NSAID use or by hormone receptor status of breast tumors	Age, school education, parity number of births, use of HRT, and history of benign breast tumor surgery	
Literature database search from 2001 to 2005 for cohort or case-control studies 10 studies were analyzed	Aspirin use vs none: 0.74 (0.69-0.79) in all studies, 0.82 (0.73-0.92) in 4 cohort studies, and 0.70 (0.56-0.87) in 6 case-control studies	N/A	
Self-administered questionnaire	Low-dose aspirin has no preventive effect of breast cancer in the subgroup analysis by tumor characteristics at diagnosis	None	

significant dose-response relationship. The protective effect was similar when cohort and case-control studies were examined separately (120, 121). Similar results were observed in two literature-based meta-analyses (122, 160).

Most observational studies and meta-analyses showed consistent and statistically significant risk reductions in human breast cancer with exposure to NSAIDs; however, interpretation of the existing body of literature on the associations between various NSAIDs and breast cancer risk is not straightforward. Although most studies on this topic have shown 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, studies using only prescription records or health plan data will misclassify over-the-counter medication users as unexposed and thereby may underestimate exposure prevalence. Four large follow-up studies (82, 115, 150, 151) found no evidence of reduced risk of breast cancer among aspirin users, yet the majority of cohort studies found significant risk reductions among aspirin users (83, 139-141, 144-146, 148, 153). Importantly, however, two randomized trials, considered the gold standard in epidemiologic study designs, did not show a chemoprotective effect of aspirin use. It is possible, as suggested by Jacobs et al. (119) that higher-dose aspirin preparations may be needed to produce a chemoprotective effect. However, because they are the most common cause of serious gastrointestinal complications in the United States (161-163), chemopreventive trial of adult-dose (e.g., 325 mg) aspirin might be problematic. It is also possible that selective COX-2 inhibitors have much stronger chemopreventive properties than aspirin. Although previous trials revealed the serious side effects related to cardiovascular events with these drugs (164-166), recent reviews and meta-analyses of controlled observational studies (167) and randomized trials (123) confirmed that only rofecoxib was associated with the risk of cardiovascular events and suggests that celecoxib and other COX-2 inhibitors in commonly used doses may not increase the risk. Thus, additional randomized trials with these COX-2 inhibitors may be needed to resolve these questions. In conclusion, although the lack of a protective effect of aspirin in randomized trials is somewhat worrisome, the overwhelming majority of the existing evidence points to a chemoprotective role of aspirin in breast cancer etiology.

Conclusions and Future Directions

The existing literature on the use of common over-the-counter and prescription medications has not definitively 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 methodologic issues, discussed throughout this review, associated with the various study designs employed in these investigations. Thus, in conclusion, 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 significant chemoprotective evidence implicating aspirin use against breast cancer. Future studies with detailed lifetime medication histories are needed to further clarify these important associations. 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 epidemiologic studies that link prolonged higher-dose aspirin use to reduce risk of breast cancer, a chemoprevention trial of NSAIDs or COX-2 inhibitors with similar chemopreventive properties to aspirin but without severe adverse gastrointestinal effects might be warranted. As pointed out above, medication use constitutes a ubiquitous exposure in the United States and in many countries

worldwide. Given that breast cancer is the most common cancer in the United States and elsewhere, it is essential that we increase our understanding on the role of these commonly used drugs in the etiology of this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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