Short Communication

Nonsteroidal Anti-inflammatory Drug Use and Breast Cancer Risk[1]

Michelle Cotterchio,[2] Nancy Kreiger, Margaret Sloan, and Allan Steingart

Division of Preventive Oncology, Research Unit, Cancer Care Ontario [M. C., N. K., M. S.], and Departments of Public Health Sciences [M. C., N. K.] and Psychiatry [A. S.], University of Toronto, Toronto, Ontario, M5G 2L7 Canada

Abstract

Findings from previous epidemiological studies are inconclusive, though they suggest nonsteroidal anti-inflammatory drug (NSAID) use is associated with a reduction in breast cancer risk. In addition, animal studies report that NSAIDs inhibit mammary tumor development. The association between NSAID use and breast cancer risk was evaluated using a case-control study design. Cases were a random sample of women diagnosed with a first primary cancer of the breast, aged 25–74 years, identified through the Ontario Cancer Registry, and diagnosed between July 1996 and September 1998. Controls were an age-matched random sample of the female population of Ontario. Cases (n = 3133) and controls (n = 3062) completed a mailed questionnaire with information on their past use of NSAID and other medications, as well as many risk factors thought to be associated with breast cancer. Multivariate logistic regression analysis was used to obtain adjusted odds ratio (OR) estimates. Use of any NSAID medication (daily use for ≥2 months) was found to be associated with a significant 24% reduction in breast cancer risk (OR = 0.76; 95% confidence interval: 0.66, 0.88). The reduced risk was strongest for use lasting >8 years, compared with nonusers (OR = 0.68; 95% confidence interval: 0.54, 0.86). No marked trends were observed for time since first use or last use or age at first use. Our results suggest a reduction in breast cancer risk associated with any regular NSAID use. NSAID use is a modifiable factor, and any protective effect attributed to its use could be of great public health importance.

Introduction

Breast cancer is a major health concern, yet little is known about its primary prevention, and established risk factors account for fewer than half of all breast cancer cases (1). NSAIDs[3] are predominantly used to treat arthritis and general pain, although recently, they have received attention regarding their potential as chemopreventive agents for diseases such as colorectal cancer and heart disease (2–4). Epidemiological studies are inconclusive, but they suggest NSAID use may be associated with a reduced breast cancer risk, and animal studies support the hypothesis that NSAIDs inhibit the development of mammary tumors.

The majority of case-control and cohort studies conducted to date, including the National Health and Nutrition Examination Survey, reported a reduced breast cancer risk associated with NSAID use (5–8), whereas other studies, including the Nurses Health Study, found no association (9, 10). For decades, animal studies have shown that NSAIDs inhibit the development of mammary tumors (11–14). NSAIDs may protect against the development of certain cancers by inhibiting COX, an enzyme involved in the biosynthesis of prostaglandin (local hormone), which is thought to promote cell proliferation and tumor development (15–18). In addition, NSAIDs have been shown to increase apoptosis (programmed cell death), which protects against the development of cancer (19).

It is important to clarify the relationship between NSAID use and breast cancer risk because, if protective, this would be of great public health significance. Our study evaluated the association between NSAID use and subsequent breast cancer risk among 6000 women participating in a population-based, case-control study in Ontario.

Materials and Methods

Cases and Controls. Cases were a random sample of women diagnosed with a first primary cancer of the breast (pathology report confirmed), aged 25–74 years, identified through the OCR, and diagnosed in the period July 1996 to September 1998. Because of the high volume of breast cases diagnosed each year (n = ~4400), cases were randomly sampled, using a 50% sampling fraction, throughout this 2-year period to reduce the study's workload. The OCR registers all cases of invasive cancer diagnosed among all residents of Ontario using computerized probabilistic record linkage to resolve the four main sources of cancer information. These four data sources are: (*a*) pathology reports with any mention of cancer; (*b*) hospital discharge summaries which include a diagnosis of cancer; (*c*) reports from Ontario's regional cancer centers; and (*d*) death certificates. Over 95% of pathology reports relating to breast cancer in Ontario are received by the OCR, nearly all within 3 months of biopsy (20). Controls were an age-stratified random sample of women identified using the 1996 population-based assessment rolls of the Ontario MOF. Controls were randomly selected and 1:1 frequency matched, within 5-year age groups, to the breast cancer cases. The Ontario MOF assessment roll database fields include full name, age, sex, and address for all

Received 2/1/01; revised 7/12/01; accepted 8/17/01.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported by the Canadian Breast Cancer Research Initiative.
[2] To whom requests for reprints should be addressed, at Division of Preventive Oncology, Cancer Care Ontario, 620 University Avenue, Toronto, Ontario, M5G 2L7 Canada. Phone: (416) 971-5100, extension 1205; Fax: (416) 971-7554; E-mail: michelle.cotterchio@cancercare.on.ca.
[3] The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; OCR, Ontario Cancer Registry; MOF, Ministry of Finance; OR, odds ratio; HRT, hormone replacement therapy; BMI, body mass index; MVOR, multivariate-adjusted odds ratio; CI, confidence interval; ASA, acetyl-salicylic acid.

home owners and tenants in Ontario. A reabstraction study was able to link >95% of persons in the OCR to the MOF database, suggesting that the accuracy of the completed MOF database fields is high (21).

Data Collection. Physicians identified in the pathology reports were asked to give consent to contact their patient and to provide the patient address, telephone number, and vital status. Cases and controls were mailed a self-administered questionnaire that included questions about their past use of NSAIDs and other medications (colored pill photographs were included), as well as information on many potential confounders. The questionnaire asked about ever use of NSAIDs (defined as daily use for >2 months), as well as the name of the medication, age started, age stopped, and total duration of use. Photographs of 12 different NSAIDs (and relevant doses) were included in the questionnaire (*e.g.*, entrophen, novasen, aspirin, ibuprofen/Motrin, voltaren, novo-methacin, naproxen, and piroxicam), and there was also a question about the use of any medications not listed. A $5 financial incentive was included in the control mailings, in an effort to improve response rates (22). In ≤2 weeks of questionnaire mailing, a follow-up postcard was sent to remind/thank all women. Nonresponders were followed up with a telephone call 4 weeks later.

Data Analysis. Multivariate logistic regression analysis was performed to obtain OR estimates for NSAID use while simultaneously adjusting for identified confounders (23). Statistical analysis was performed using EGRET (24). Potential confounders (>20) were evaluated using the 10% change-in-estimate method (25); only age, history of arthritis, and benign breast disease remained in the final multivariate models. Variables that were evaluated for confounding included: HRT, oral contraceptive use, alcohol consumption, smoking, weight, BMI, physical activity, history of arthritis, reproductive history (including age at menarche, age at menopause, child bearing, and breast feeding), education, marital status, previous breast cysts, family history of breast cancer, other medication use, and dietary fat intake. The possibility of interactions between NSAID use and other variables was assessed by the statistical significance of the likelihood ratio statistic ($P < 0.05$) after the addition of the product term(s) to the model (26). Variables assessed for interaction with NSAID use included BMI, HRT, dietary fat, and menopausal status. NSAID use reported in the 1-year period before the breast cancer diagnosis date (or referent date for controls) was excluded from the analysis.

The response rate was 73% (3133 of 4289) for cases and 61% (3062 of 5001) for controls. Reasons for nonparticipation included language barrier, illness, too busy, and privacy concerns; however, the majority of both cases and controls did not provide a reason. Breast cancer cases (>95%) were adenocarcinoma/carcinoma, with the two most common histologies being infiltrating duct carcinoma (78%) and lobular carcinoma (8%). The average length of time between breast cancer diagnosis and completion of the questionnaire was 10 months (range was 1–33 months).

Results

Table 1 shows the frequency distribution of breast cancer cases and controls and age-adjusted OR estimates for established breast cancer risk factors. As expected, family history of breast cancer, personal history of benign breast cysts, and higher education level were associated with an increased risk of breast cancer, and late menopause was associated with a slight increase in risk. Both a later age at menarche and increased parity were associated with a decreased risk of breast cancer, whereas marital status was not associated with breast cancer risk.

Table 2 shows the frequency distribution, MVOR estimates, and 95% CIs for any regular NSAID use, NSAID drug subgroups (ASAs and non-ASAs), tertiles of NSAID use duration, time since first and last use, and age at first use. Regular NSAID use was associated with a statistically significant decreased breast cancer risk (MVOR = 0.76; 95% CI: 0.66, 0.88). The observed reduction in risk was not markedly different for ASA and non-ASA drugs. A small reduction in risk was observed for any duration of use, although this association was of greatest magnitude and statistical significance for use lasting >8 years (MVOR = 0.68; 95% CI: 0.54, 0.86). Compared with never users, a similar reduction in risk was seen regardless of time since first using NSAIDs and age at first use. Similarly, no trend in risk was observed for time since last use, and the statistical significance of the OR associated with current NSAID use may be attributable to the increased sample size in this category.

Associations between NSAID use (*e.g.*, duration and age at first use) and breast cancer risk were also assessed within strata defined by menopausal status; there were no differences between pre and postmenopausal women (data not shown). In addition, dietary fat intake, BMI, and HRT use were not found to be statistically significant effect modifiers of the association between any NSAID use and breast cancer risk, although the observed reduction in breast cancer risk among NSAID users was diminished slightly among women who did not use HRT (HRT users: OR = 0.73, 95% CI: 0.58, 0.94; HRT nonusers: OR = 0.87, 95% CI: 0.69, 1.09; interaction likelihood ratio statistic $P = 0.10$).

NSAID users (71%) reported a diagnosis of arthritis compared with only 25% of women that did not use NSAIDs regularly; however, arthritis was not found to be associated with breast cancer risk in our data set (data not shown). The association, among control subjects, between NSAID use and known breast cancer risk factors is as follows (data not shown): variables positively associated with NSAID use include age, family history of breast cancer, smoking, BMI, benign breast cysts, parity, early menopause, and HRT use; variables negatively associated with NSAID use include education and marital status; variables not associated with NSAID use (χ^2 $P > 0.05$) include alcohol intake, dietary fat intake, and physical activity.

Discussion

This population-based study, conducted specifically to evaluate the use of certain medications and breast cancer risk, found a small reduction in breast cancer risk among women who had used NSAIDs. Previous epidemiological studies to evaluate the association between NSAID use and breast cancer risk have produced inconsistent results, though the majority of evidence suggests NSAID use is associated with a reduction in risk. As NSAID use is a modifiable factor, any protective effect attributed to its use could be of great public health importance.

Consistent with our findings, several large epidemiological studies reported a decreased risk of breast cancer among aspirin users (5, 7, 8, 27). The National Health and Nutrition Examination Survey I study obtained limited information from women regarding their recent aspirin use, and these women were then followed for an average of 12 years (5). Unlike our study which found no association with age at first use, however, Schreinemachers and Everson (5) observed that the reduction in breast cancer risk was mostly attributable to the effect seen among women <50 years at the start of the study (RR = 0.5;

Table 1 Distribution of breast cancer cases and controls and AOR[a] estimates for several established breast cancer risk factors and subject characteristics

Variable	Cases (n = 3133)		Controls (n = 3062)		AOR
	No.[b]	(%)	No.[b]	(%)	
Breast cancer in first-degree relative[c]					
No	2433	(82)	2527	(89)	1.0
Yes	521	(18)	308	(11)	1.72 (1.48, 2.00)
Benign breast cysts					
No	1312	(45)	2185	(75)	1.0
Yes	1621	(55)	720	(25)	3.71 (3.32, 4.15)
Age at menarche					
≤11	588	(19)	540	(18)	1.0
12	788	(26)	733	(24)	0.99 (0.85, 1.16)
13	907	(29)	880	(29)	0.94 (0.81, 1.09)
≥14	806	(26)	868	(29)	0.83 (0.71, 0.97)
Parity[d]					
Nulliparous	461	(15)	377	(12)	1.0
1	398	(13)	357	(12)	0.94 (0.77, 1.16)
2–3	1725	(56)	1673	(55)	0.85 (0.72, 1.01)
≥4	520	(17)	629	(21)	0.64 (0.52, 0.77)
Age at menopause[e]					
<45	612	(21)	647	(23)	1.0
45–49	550	(19)	531	(19)	1.09 (0.93, 1.28)
≥50	903	(31)	736	(26)	1.27 (1.09, 1.48)
Premenopausal	859	(29)	949	(33)	—
HRT use[f]					
No	1235	(40)	1128	(37)	1.0
Yes	996	(32)	946	(31)	0.96 (0.85, 1.09)
Premenopausal	859	(28)	949	(31)	N/A[a]
Age group					
25–39	210	(7)	264	(9)	N/A
40–44	275	(9)	288	(9)	N/A
45–49	420	(13)	393	(13)	N/A
50–54	469	(15)	517	(17)	N/A
55–59	461	(15)	318	(14)	N/A
60–64	453	(15)	388	(13)	N/A
65–69	469	(15)	440	(14)	N/A
70–74	376	(12)	354	(12)	N/A
Highest level of education					
Elementary	399	(13)	426	(14)	1.0
High school	1469	(47)	1386	(46)	1.18 (1.01, 1.38)
Postsecondary	1246	(40)	1221	(40)	1.19 (1.00, 1.40)
Marital status					
Currently married	2319	(74)	2293	(75)	1.0
Widow/separated/divorced	797	(26)	747	(25)	1.04 (0.92, 1.17)

[a] AOR, age-adjusted OR; N/A, nonapplicable.
[b] Numbers may not add to total because of missing values.
[c] Mother, sister, or daughter.
[d] Live births.
[e] Last menstrual period.
[f] Hormone replacement therapy for at least 2 months.

95% CI: 0.3, 0.9). Unfortunately, information on duration of use was not obtained in that study, and only a limited number of potential confounders were assessed. Coogan *et al.* (6) evaluated the association between regular NSAID use (more than or equal to four times per week for 3 months) and breast cancer risk using data from a large hospital-based, case-control surveillance study that was initiated in the mid-1970s. With non-cancer controls as the comparison group, regular NSAID use was associated with a significantly reduced breast cancer risk (OR = 0.7; 95% CI: 0.6, 0.9), which was strongest with long duration of use. Contrary to our finding that ASA and non-ASA drugs were associated with a similar decreased risk, the reduction in risk observed in Coogan *et al.*'s study (6) was more pronounced among aspirin (ASA) users. The authors caution that inconsistencies in their results across study centers, years, and control groups weaken the validity of these findings. Harris *et al.* (8) reported a significant halving of risk conferred by weekly use of either ASA or non-ASA NSAIDs among a large cohort of women enrolled in a mammography screening program and followed for an average of 5 years, a result which is comparable with our findings. As well, two earlier case-control studies conducted by Harris *et al.* (7, 27) found a reduction in breast cancer risk associated with any regular NSAID use for >1 year; these hospital/clinic-based studies, however, may have been biased because the controls could be more likely to use NSAIDs than the general population.

Although the effect modification was not statistically significant, in contrast to Harris et al. (8) who reported a diminished protective among HRT users (*versus* nonusers), we observed that the reduction in breast cancer risk associated with

Table 2 MVOR estimates and 95% CI for any regular NSAID use and various aspects of regular NSAID use[a]

	Cases		Controls		MVOR[c] (95% CI)
	No.[b]	(%)	No.[b]	(%)	
Any regular NSAID use					
Never	2306	(76)	2182	(74)	1.0
Ever	742	(24)	786	(26)	0.76 (0.66, 0.88)
ASA/non-ASA use					
Never	2306	(77)	2182	(75)	1.0
ASA	390	(13)	418	(14)	0.73 (0.61, 0.87)
Non-ASA[d] only	316	(10)	330	(11)	0.79 (0.66, 0.96)
Duration of NSAID use (yrs)					
Never	2306	(80)	2182	(78)	1.0
≤1	153	(5)	173	(6)	0.77 (0.59, 0.98)
2–8	226	(8)	232	(8)	0.78 (0.63, 0.98)
≥9	199	(7)	229	(8)	0.68 (0.54, 0.86)
Time since last NSAID use (yrs)					
Never	2306	(82)	2182	(78)	1.0
≤1 (current use)	387	(14)	469	(17)	0.64 (0.54, 0.77)
2–6	65	(2)	67	(2)	0.76 (0.52, 1.10)
≥7	62	(2)	67	(2)	0.75 (0.51, 1.10)
Time since first NSAID use (yrs)					
Never	2306	(79)	2182	(77)	1.0
2–7	195	(7)	208	(7)	0.77 (0.61, 0.98)
8–16	198	(7)	212	(8)	0.73 (0.58, 0.92)
≥17	218	(8)	226	(8)	0.73 (0.58, 0.91)
Age at first use					
Never	2306	(74)	2182	(72)	1.0
≤43	265	(8)	299	(10)	0.69 (0.57, 0.85)
44–49	282	(9)	281	(9)	0.82 (0.66, 1.00)
≥50	280	(9)	300	(10)	0.76 (0.61, 0.93)

[a] Defined as taken daily for at least 2 months.
[b] Numbers may not add to total because of missing values.
[c] Adjusted for age, arthritis, and benign breast cysts.
[d] Includes propionic acids, acetic acids, and oxicams.

NSAID use was diminished slightly among non-HRT users. Additional investigation of the hypothesized link between NSAIDs, prostaglandin, and estrogen biosynthesis may shed light on these findings (28, 29).

In contrast to other studies, the Nurses' Health Study reported no association between aspirin use (more than or equal to two per week) and breast cancer risk after 12 years of follow-up (RR = 1.0; 95% CI: 1.0, 1.1; Ref. 9). Detailed information on aspirin use, as well as the update of exposures throughout the follow-up period, strengthens the validity of these findings, although information on aspirin use was not available for the last 4 years of follow-up. Random misclassification of recency of use, observed to be associated with decreased cancer risk in our current findings, may have biased that study's relative risk estimates toward the null. Furthermore, if, as we found, both ASA (*e.g.,* aspirin) and non-ASA drugs have a similar protective effect, studies that consider only aspirin use may introduce nondifferential misclassification and fail to detect an association between NSAIDs and cancer risk.

It is unlikely that general over-reporting of medication use by the control subjects is responsible for the protective effect seen in our study, because in our data, other medication use (*e.g.,* antidepressants) was found to be associated with a slight increase in breast cancer risk (30). However, it is perhaps plausible that health conscious controls taking NSAIDs to prevent heart disease were more likely to participate, biasing the OR (protective) away from the null. Our observation that a lower (*versus* higher) education was associated with NSAID use in our data set casts doubt on this possibility. Survival bias may be a concern in case-controls studies; Schapira *et al.* (31) reported that NSAID use may favorably affect the prognosis of breast cancer. If cases who used NSAIDs have improved survival, they could be over-represented in our study, biasing our findings toward the null. Because both our cases and controls were selected from population-based sampling frames, selection bias is unlikely. Furthermore, known risk factors were found to be associated with breast cancer risk in our data set. We evaluated, and adjusted for, possible confounding attributable to known breast cancer risk factors. Although we lacked data on indication for NSAID use, there is no evidence that conditions associated with NSAID use have any association with breast cancer risk.

Several plausible biological mechanisms support the hypothesis that NSAIDs may have chemopreventive ability with regard to breast cancer. Recently, animal models have shown that NSAIDs are capable of triggering apoptosis (death) in neoplastic mammary cells, thereby protecting against the development of cancer (19). Additional research is needed to help elucidate the involvement of NSAIDs in the apoptotic pathway. As well, it is known that NSAIDs prevent prostaglandin production by inhibiting the COX enzymes, thus decreasing the opportunity for prostaglandin to promote tumor development (15, 16). Several studies have shown that the level of prostaglandin in tumors is greater than that of normal tissue (32, 33). Furthermore, COX enzyme expression has been shown to be substantially increased in human breast cancer tissue compared with normal breast tissue, suggesting its involvement in the development of breast cancer (34). There are two COX isoforms, COX-1 and COX-2, and whether inhibition of one or both is required for the protective effect of NSAIDs remains

unknown. Until recently, all NSAIDs inhibited both COX-1 and -2 enzymes. Recently, selective COX-2 inhibitors have been developed and widely marketed as an NSAID with fewer gastrointestinal side effects. The chemopreventive ability of these drugs will need to be assessed in future breast cancer studies as selective COX-2 inhibitors were not yet available at the start of our study.

Acknowledgments

We thank the efforts of all of the Women's Health Study staff. We especially thank the study coordinators, Erin Smith and Gabrielle Rabbat, for their dedication to this study. We also thank Lori-Ann Larmand, Gayle Morrison, Elana Steingart, and Giao Buchan for their assistance with data cleaning and Gerarda Darlington for her contribution to the development of this research.

References

1. Madigan, M. P., Zeigler, R. G., Benichou, J., Byrne, C., and Hoover, R. N. Proportion of breast cancer cases in the United States explained by well-established risk factors. J. Natl. Cancer Inst. (Bethesda), *87:* 1681–1685, 1995.

2. Krishnan, K., Ruffin, M. T., and Brenner, D. E. Colon cancer chemoprevention: clinical development of aspirin as a chemopreventive agent (review). J. Cell. Biochem. Suppl., *28:* 148–158, 1997.

3. Giovannucci, E. The prevention of colorectal cancer by aspirin use. Biomed. Pharmacother., *53:* 303–308, 1999.

4. Meade, T., and Brennan, P. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised control trial. Br. Med. J., *321:* 13–17, 2000.

5. Schreinemachers, D. M., and Everson, R. B. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology, *5:* 138–146, 1994.

6. Coogan, P. F., Rao, R. S., Rosenberg, L., Palmer, J. R., Strom, B. L., Zauber, A. G., Stolley, P. D., and Shapiro, S. The relationship of nonsteroidal anti-inflammatory drug use to the risk of breast cancer. Prev. Med., *29:* 72–76, 1999.

7. Harris, R. E., Namboodiri, K. K., and Farrar, W. B. Nonsteroidal anti-inflammatory drugs and breast cancer. Epidemiology, *7:* 203–205, 1996.

8. Harris, R. E., Kasbari, S., and Farrar, W. B. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. Oncol. Rep., *6:* 71–73, 1999.

9. Egan, K. M., Stampfer, M. J., Giovannucci, E., Rosner, B. A., and Colditz, G. A. Prospective study of regular aspirin use and the risk of breast cancer. J. Natl. Cancer Inst. (Bethesda), *88:* 988–993, 1996.

10. Rosenberg, L. Nonsteroidal anti-inflammatory drugs and cancer. Prev. Med., *24:* 107–109, 1995.

11. McCormick, D., Madigan, M., and Moon, R. Modulation of rat mammary carcinogensis by indomethacin. Cancer Res., *45:* 1803–1808, 1985.

12. McCormick, D., and Wilson, A. Combination chemoprevention of rat mammary carcinogenesis by indomethacin and butylated hydroxytoluene. Cancer Res., *46:* 3907–3911, 1986.

13. Mehta, R., and Moon, R. Characterization of effective chemopreventive agents in mammary gland *in vitro* using an initiating-promotion protocol. Anticancer Res., *11:* 593–596, 1991.

14. Abou-Issa, H., Alshafie, A., Seibert, K., and Harris, R. Chemoprevention of breast cancer in rats by celecoxib, a COX-2 inhibitor. Proc. Am. Assoc. Cancer Res., *41:* 493, 2000.

15. Marnett, L. J. Aspirin and related nonsteroidal anti-inflammatory drugs as chemopreventive agents against colon cancer. Prev. Med., *24:* 103–106, 1995.

16. Szarka, C. E., Grana, G., and Engstrom, P. F. Chemoprevention of cancer. Curr. Prob. Cancer, *18:* 6–79, 1994.

17. Turner, D., and Berkel, H. J. Nonsteroidal anti-inflammatory drugs for the prevention of colon cancer. CMAJ, *149:* 595–602, 1993.

18. Wolfle, D., Marotzki, S., Dartsch, D., Schafer, W., and Marquardt, H. Induction of cyclooxygenase expression and enhancement of malignant cell transformation by 2,3,7,8-tetrachlorodibenzop-dioxin. Carcinogenesis (Lond.), *21:* 15–21, 2000.

19. Thompson, H. J., Jiang, C., Lu, J., Mehta, R. G., Piazza, G. A., Paranka, N. S., Pamukcu, R., and Ahnen, D. J. Sulfone metabolite of suldinac inhibits mammary carcinogenesis. Cancer Res., *57:* 267–271, 1997.

20. Robles, S., Marrett, L., Clarke, E., and Risch, H. An application of capture-recapture methods to the estimation of completeness of cancer registries. J. Clin. Epidemiol., *41:* 495–501, 1988.

21. Holowaty, E. J., Lee, G., Dale, D., and Chong, N. A reabstraction study to estimate the accuracy and completeness of data elements in the Ontario Cancer Registry. American Association of Central Cancer Registries. Niagara-on-the-Lake, Ontario, 1994.

22. Gilbart, E., and Kreiger, N. Improvements in cumulative response rates following implementation of financial incentive. Am. J. Epidemiol., *148:* 97–99, 1998.

23. Schlesselman, J. J. (ed.). Case-control Studies: Design, Conduct, Analysis. Oxford, United Kingdom: Oxford University Press, 1982.

24. Cytel Software Corporation EGRET, Cambridge, Massachusetts, 1999.

25. Maldonado, G., and Greenland, S. Simulation study by confounder-selection strategies. Am. J. Epidemiol., *138:* 923–936, 1993.

26. Greenland, S. Modeling and variable selection in epidemiologic analysis. Am. J. Public Health, *79:* 340–349, 1989.

27. Harris, R. E., Namboodiri, K., Stellman, S. D., and Wynder, E. L. Breast cancer and NSAID use: heterogeneity of effect in a case control study. Prev. Med., *24:* 119–120, 1995.

28. Zhao, Y., Agarwal, V., Mendelson, C., and Simpson, E. R. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. Endocrinology, *137:* 5739–5742, 1996.

29. Harris, R. E., Robertson, F. M., Abou-Issa, H. M., Farrar, W. B., and Brueggemeier, R. Genetic induction and upregulation of cyclooxygenase (COX) and aromatase (CYP19): an extension of the dietary fat hypothesis of breast cancer. Med. Hypotheses, *52:* 291–292, 1999.

30. Kreiger, N., Cotterchio, M., Steingart, A., and Buchan, G. Antidepressant medication use and breast cancer risk. Am. J. Epidemiol., *151:* S27, 2000.

31. Schapira, D. V., Theodossiou, C., and Lyman, G. H. The effects of NSAIDs on breast cancer prognostic factors. Oncol. Rep., *6:* 433–435, 1999.

32. Rolland, P. H., Martin, P. M., Jacquemier, J., Rolland, A. M., and Toga, M. Prostaglandin in human breast cancer: evidence suggesting that an elevated prostaglandin production is a marker of high metastatic potential for neoplastic cells. J. Natl. Cancer Inst. (Bethesda), *64:* 1061–1070, 1980.

33. Levine, L. Arachidonic acid transformation and tumor production. Adv. Cancer Res., *35:* 49–79, 1981.

34. Hwang, D., Scollard, D., Byrne, J., and Levine, E. Expression of cyclooxygenase-1 and cyclooxygenase-2 in human breast cancer. J. Natl. Cancer Inst. (Bethesda), *90:* 455–460, 1998. Supported by the Canadian Breast Cancer Research Initiative.

Nonsteroidal Anti-inflammatory Drug Use and Breast Cancer Risk

Michelle Cotterchio, Nancy Kreiger, Margaret Sloan, et al.

Cancer Epidemiol Biomarkers Prev 2001;10:1213-1217.