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1. STUDIES PUBLISHED BEFORE 1999 NOT IN THE IARC REVIEW

1.1 Thun, M. J., M. M. Namboodiri, et al. (1993). "Aspirin use and risk of fatal cancer."

Cancer Res 53(6): 1322-1327.

Aspirin and other nonsteroidal antiinflammatory drugs inhibit prostaglandin synthesis and tumor growth in many experimental systems, but it is unclear which of these tumor models are relevant to humans. We have reported reduced risk of fatal colon cancer among persons who used aspirin in a large prospective study. This analysis examines other fatal cancers in relation to aspirin among 635,031 adults in that study who provided information in 1982 on the frequency and duration of their aspirin use and did not report cancer. Death rates were measured through 1988. Death rates decreased with more frequent aspirin use for cancers of the esophagus, stomach, colon, and rectum but not generally for other cancers. For each digestive tract cancer, death rates were approximately 40% lower among persons who used aspirin 16 times/month or more for at least 1 year compared to those who used no aspirin. The trend of decreasing risk with more frequent aspirin use was strongest among persons who had used aspirin for 10 years or more; it remained statistically significant, except for esophageal cancer, in multivariate analyses that adjusted for other known risk factors. Biases such as early detection or aspirin avoidance among cases do not appear to explain the results. Our data suggest that regular, prolonged use of aspirin may reduce the risk of fatal cancer of the esophagus, stomach, colon, and rectum. Future epidemiological and basic research should examine all digestive tract cancers in considering the chemopreventive or therapeutic potential of nonsteroidal antiinflammatory drugs.

*[There were no results for acetaminophen in the abstract. Example of text in article: "**Rectum cancer** mortality was significantly higher in men and women who used **acetaminophen** 16 times/month or more compared to those who used neither aspirin nor acetaminophen (relative risk, 3.08; 95% confidence interval, 1.11-8.54).]*

1.2 Muscat, J. E., S. D. Stellman, et al. (1994). "Nonsteroidal antiinflammatory drugs and colorectal cancer."

Cancer 74(7): 1847-1854.

BACKGROUND. The association between the use of nonsteroidal antiinflammatory drugs (NSAID) and large bowel cancer was examined in a

hospital-based case-control study of 511 patients with **colorectal cancer** and 500 age-sex matched control subjects. METHODS. Regular NSAID use was defined as at least 3 times per week for 1 or more years before the date of hospital admission. Odds ratios (OR) were calculated by the duration of NSAID use and according to the medical reasons given for taking NSAIDs. RESULTS. The prevalences of regular NSAID use were 15% for male patients, 8% for female patients, and 20% for control subjects. Overall, NSAID use was associated with a statistically significant risk reduction in men (OR = 0.64; 95% confidence interval [CI], 0.42-0.97) and in women (OR = 0.32; 95% CI, 0.18-0.57). The estimate decreased with duration among men but increased with duration among women. The risk reduction among patients who took NSAIDs to prevent heart disease was 0.67 (95% CI, 0.38-1.13) for men and 0.43 (95% CI, 0.12-1.59) for women. For treating headache pain, the OR was 0.5 (95% CI, 0.23-1.09) for men and 0.64 (95% CI, 0.25-1.62) for women. The use of NSAID was not found to be associated with the stage of cancer at diagnosis. The OR for daily **acetaminophen** use was 1.07 (95% CI, 0.35-3.23) for men and 0.59 (95% CI, 0.27-1.25) for women. CONCLUSIONS. The regular use of NSAIDs was associated with an overall significant risk reduction of colorectal cancer in men and in women. Among female patients, the greater protective effect associated with short term NSAID use compared with long term NSAID use may reflect a sampling bias.

1.3 Peleg, II, H. T. Maibach, et al. (1994). "Aspirin and nonsteroidal anti-inflammatory drug use and the risk of subsequent colorectal cancer."

Arch Intern Med 154(4): 394-399.

OBJECTIVE: To test the hypothesis that the regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is negatively associated with the risk of subsequent colorectal cancer. DESIGN: Case-control study with four age- and sex-matched control subjects for each incident colorectal cancer case. POPULATION AND SETTING: Patient population of a large municipal teaching hospital in Atlanta, Ga. MAIN OUTCOME MEASURE: Odds of colorectal cancer as a function of aspirin, nonaspirin NSAIDs, and acetaminophen dispensed to the study population in the 4 years prior to incident colorectal cancer diagnosis. MAIN RESULTS: The risk of **colorectal cancer** estimated by odds ratios decreased with increasing days of exposure to aspirin linearly in a dose-dependent fashion (likelihood ratio statistic: for cumulative days, P < .001; for cumulative dose, P < .001). The coefficient for days of exposure to aspirin was highly significant even when modeled as a continuous variable (P = .001). There appeared to be a threshold above which nonaspirin NSAIDs afforded protection (likelihood ratio statistic: for cumulative days, P = .021; for cumulative dose, P = .019). **Acetaminophen** conferred no risk reduction. CONCLUSION: The results of previous experimental animal models, interventional case studies, and some but not all epidemiological investigations

and the present data point toward a causal relationship between NSAID use and the prevention of cancer of the large bowel and rectum. Because of the potential gastrointestinal and renal side effects of NSAID use, particularly in the elderly, chemoprevention trials are now needed to allow risk-benefit analysis in populations at high risk for colorectal cancer.

1.4 Rodriguez, C., S. J. Henley, et al. (1998). "Paracetamol and risk of ovarian cancer mortality in a prospective study of women in the USA." (letter)

Lancet 352(9137): 1354-1355.

*[Letter. Says: "We examined the association between use of paracetamol (Tylenol) and death rates from ovarian cancer in a prospective study," and "Women who reported using **paracetamol** daily had a 45% lower death rate from **ovarian cancer** than women reporting no use (RR=0·55, 95% CI=0·27–1·09)."]*

2. STUDIES PUBLISHED AFTER THE IARC REVIEW

2.1 Gago-Dominguez, M., J. M. Yuan, et al. (1999). "Regular use of analgesics is a risk factor for renal cell carcinoma"

Br J Cancer 81(3): 542-8.

Phenacetin-based analgesics have been linked to the development of renal pelvis cancer and **renal cell carcinoma (RCC)**. The relationship between non-phenacetin types of analgesics and kidney cancer is less clear, although laboratory evidence suggests that these drugs possess carcinogenic potential. A population-based case-control study involving 1204 non-Asian RCC patients aged 25-74 and an equal number of sex-, age- and race-matched neighbourhood controls was conducted in Los Angeles, California, to investigate the relationship between sustained use of analgesics and risk of RCC according to major formulation categories. Detailed information on medical and medication histories, and other lifestyle factors was collected through in-person interviews. Regular use of analgesics was a significant risk factor for **RCC** in both men and women (odds ratio (OR) = 1.6, 95% confidence interval (CI) = 1.4-1.9 for both sexes combined). Risks were elevated across all four major classes of analgesics (aspirin, non-steroidal anti-inflammatory agents other than aspirin, **acetaminophen** and phenacetin). Within each class of analgesics, there was statistically significant increasing risk with increasing level of exposure. Although there was some minor variability by major class of formulation, in general individuals in the highest exposure categories exhibited approximately 2.5-fold increase in risk relative to non- or irregular users of analgesics. Subjects who took one regular-strength (i.e. 325 mg) aspirin a day or less for cardiovascular disease prevention were not at an increased risk of RCC (OR = 0.9, 95% CI = 0.6-1.4).

2.2 Pommer, W., E. Bronder, et al. (1999). "Urothelial cancer at different tumour sites: role of smoking and habitual intake of analgesics and laxatives. Results of the Berlin Urothelial Cancer Study"

Nephrol Dial Transplant 14(12): 2892-7.

BACKGROUND: In Germany about 20000 new cases of urothelial cancer (UC) and about 7500 deaths from bladder cancer alone occur each year. Among the manifold risk factors, little research has been done on the role of smoking and the habitual intake of analgesics and laxatives-practices that are common in parts of the German population. The aim of this study is to define the proportion of risk derived from these preventable habits for the development of UC at its different sites. Subjects and methods. A case-control study in the area of the former West Berlin was performed from 1990 to 1995 including all newly diagnosed incident cases of UC from the eight hospitals of the study area. Study subjects and population-based controls individually matched by age (+/-2 years) and sex were evaluated by a standardized face-to-face interview about the lifelong exposure to cigarette smoking, analgesics, and laxatives. Adjusted risk analysis was carried out for the main exposure variables in relation to the different sites of UC in the bladder, ureter, and renal pelvis. RESULTS: Six hundred and forty-seven cases of UC (571 bladder, 25 ureter, and 51 renal pelvis) and an identical number of controls were included in the analysis (response rate in cases, 84.6%; in controls, 70.2%). Smoking increased the risk of bladder cancer (BC) by an odds ratio (OR) of 3.22 (95% confidence interval (CI) 2.29-4.52), that of ureter (URC) or **renal pelvis cancer (RPC)** together by OR 6.20 (95% CI 2.04-18.81), and that of RPC alone by OR 5.91 (95% CI 1.47-23.66). Ex-smoking was associated with an increased risk for BC (OR 1.55, 95% CI 1.10-2.19). Intake of more than 1 kg of phenacetin in analgesic mixtures was associated with an OR of 5.28 for **RPC** (intake of > or = 1 kg **paracetamol**, OR 3.27; > or = 1 kg pyrazolones, 1.12) and 0.75 for BC (not significant). Laxatives significantly increased the risk of BC (OR 2.14, 95% CI 1.26-3.63) and RPC/URC (OR 9.62, 95% CI 1. 01-91.24) in both sexes. CONCLUSION: Habitual risks from smoking and intake of laxatives significantly contribute to the development of UC, especially of the renal pelvis and ureter cancer. Intake of at least 1 kg of analgesic substances (anilides, pyrazolones) as calculated from this study base is associated with increased but not significant risks for RPC. These data underline that restrictive and educational measurements focusing on common habits would have a strong impact on preventing UC in Germany.

2.3 Castelao, J. E., J. M. Yuan, et al. (2000). "Non-steroidal anti-inflammatory drugs and bladder cancer prevention"

Br J Cancer 82(7): 1364-9.

Inclusion of phenacetin among 'proven' human carcinogens by the IARC in 1987, raised concerns about the carcinogenic potential of **acetaminophen**, its

major metabolite. Acetaminophen has been implicated as a possible causal agent in the development of cancer of the renal pelvis. The bladder and renal pelvis, which derive from the same embryological structure, share the same transitional type of epithelium. Past studies have been inconclusive on the possible relationship among these analgesics and bladder cancer but no large, highly detailed study of this association has been conducted. A population-based case-control study conducted in Los Angeles, California, involved 1514 incident bladder cancer cases and an equal number of controls who were matched to the index cases by sex, date of birth (within 5 years) and race. Detailed information on medication use and prior medical conditions was collected through in-person interviews. Regular use of analgesics was not associated with an increased risk of bladder cancer in either men or women. In fact, compared with non- or irregular users, regular analgesic users were at a decreased risk of bladder cancer overall (odds ratio (OR) = 0.81, 95% confidence interval (CI) = 0.68-0.96). However, there were clear differences in both the direction and strength of the associations between the different formulation classes of analgesics and **bladder cancer** risk. Intake of phenacetin was positively related to bladder cancer risk in a dose-dependent manner while intake of its major metabolite in humans, **acetaminophen**, was unrelated to risk. Intake of all classes of NSAIDs, except pyrazolon derivatives, were negatively associated with bladder cancer risk, with suggestive evidence that the protective effect varies in strength by subcategories of formulation. Acetic acids seemed to exhibit the strongest protective effect, whereas aspirin/other salicylic acids and oxicam showed the weakest protection.

2.4 Rosenberg, L., J. R. Palmer, et al. (2000). "A case-control study of analgesic use and ovarian cancer."

Cancer Epidemiol Biomarkers Prev 9(9): 933-7.

A recent case-control study raised the hypothesis that acetaminophen use 1 day or more per week for at least 6 months reduces the risk of epithelial ovarian cancer. We assessed analgesic use in relation to epithelial ovarian cancer risk using data from our case-control surveillance study of medication use and cancer. Patients were interviewed in hospitals in Baltimore, Boston, New York, and Philadelphia during 1976-1998. We compared 780 women with **epithelial ovarian cancer** to 2053 cancer controls and 2570 noncancer controls. For **acetaminophen** use 1 day or more per week for at least 6 months, the odds ratio estimate was 0.9 (95% confidence interval, 0.6-1.4) derived with cancer controls and 1.0 (0.6-1.5) with noncancer controls. Estimates for more frequent and longer term use were also compatible with 1.0. The odds ratios among patients with metastatic ovarian cancer were reduced but not statistically significant. The odds ratio for use of nonsteroidal anti-inflammatory drugs 4 or more days per week for at least 5 years, 0.5, was statistically significant. The present results provide only weak support for a reduction in the risk of epithelial ovarian cancer among acetaminophen users. They raise the possibility of an inverse association with long-term nonsteroidal anti-inflammatory drug use.

2.5 Kaye, J. A., M. W. Myers, et al. (2001). "Acetaminophen and the risk of renal and bladder cancer in the general practice research database."

Epidemiology 12(6): 690-4.

We conducted a nested, matched case-control study in the General Practice Research Database (GPRD) to assess whether acetaminophen use is associated with renal or bladder cancer. We matched 109 cases of renal cancer and 189 cases of bladder cancer with up to 4 controls each by age, sex, general practice, duration of drug history in the GPRD, and index date. We found that use of **acetaminophen** from 1 to 5 years before the index date was associated with an increased risk of **renal cancer**, with a direct relation between risk and number of prescriptions and an adjusted odds ratio of 2.3 (95% CI 1.0-5.3) for subjects with 20 or more prescriptions. There was no evidence for an increase in risk of **bladder cance**r with **acetaminophen** use. We found no association between use of non-steroidal anti-inflammatory drugs and either renal or bladder cancer. These results support previous findings from our group and are consistent with a slight increase in the risk of renal cancer, but not bladder cancer, with heavy acetaminophen use.

2.6 Moysich, K. B., C. Mettlin, et al. (2001). "Regular use of analgesic drugs and ovarian cancer risk."

Cancer Epidemiol Biomarkers Prev 10(8): 903-6.

Analgesics have been shown to reduce risk for colorectal cancer. Results from three recent reports (D. W. Cramer et al., Lancet, 351: 104-107, 1998; C. Rodriguez et. al., Lancet, 352: 1354-1355, 1998; L. Rosenberg et al., Cancer Epidemiol. Biomark. Prev., 9: 933-937, 2000) suggest that these drugs might be associated with decreased risk for ovarian cancer. In this hospital-based case-control study, we compared 547 patients with ovarian cancer to 1094 age-matched patients with nonneoplastic conditions. All of the participants received treatment at the Roswell Park Cancer Institute between 1982 and 1998 and completed a comprehensive epidemiological questionnaire that included information on demographics, life-style factors, and reproductive characteristics as well as frequency and duration of aspirin and acetaminophen use. Women who reported that they had used one or more of these agents at least once a week for at least 6 months were classified as analgesic users. Logistic regression was used to compute crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Aspirin users were not at reduced risk of **ovarian cancer** compared with nonusers (adjusted OR, 1.00; CI, 0.73-1.39). There was also no evidence of a decrease in risk as a function of greater frequency of use or prolonged duration of use. Regular **acetaminophen** use was associated with a reduced risk (adjusted OR, 0.56; 95% CI, 0.34-0.86), and risk reductions were observed for women with the greatest frequency of use (adjusted OR, 0.32; 95% CI, 0.09-1.08) and longest duration of use (adjusted OR, 0.51; 95% CI, 0.27-

0.97). These data suggest that regular use of acetaminophen, but not aspirin, may be associated with lower risk of ovarian cancer.

2.7 Friis, S., G. L. Nielsen, et al. (2002). "Cancer risk in persons receiving prescriptions for paracetamol: a Danish cohort study."

Int J Cancer 97(1): 96-101.

The use of paracetamol has been associated with increased risks for urinary tract cancers and decreased risk for ovarian cancer, although results have been inconsistent. We conducted a population-based cohort study using data from the Prescription Database of North Jutland County and the Danish Cancer Registry. Cancer incidence among 39,946 individuals receiving prescriptions for paracetamol was compared with expected incidence based on the North Jutland population who did not receive paracetamol prescriptions, during a 9-year follow-up period. Standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (95% CIs) were calculated for cancers overall and at selected sites. Overall, 2,173 cancers were observed with 1,973 expected, yielding a SIR of 1.10 (95% CI, 1.06-1.15). Significantly elevated SIRs were found for cancers of the esophagus (1.9; 95% CI, 1.3-2.8) and lung (1.6; 95% CI, 1.4-1.7). Nonsignificantly increased SIRs were observed for cancers of the liver (1.5; 95% CI, 0.96-2.2), renal parenchyma (1.3; 95% CI, 0.9-1.7) and renal pelvis/ureter (1.6; 95% CI, 0.96-2.6), whereas the SIR for cancer of the urinary bladder was close to unity (1.1; 95% CI, 0.9-1.4). For ovarian cancer, the SIR was close to expectation (0.9; 95% CI, 0.6-1.2) with no evidence of trends with duration of follow-up or number of prescriptions. A similar risk pattern was observed after exclusion of person-time experience following prescription for aspirin or other nonsteroidal antiinflammatory drugs in the study cohort and reference population. Our results do not support a major role for **paracetamol** in the development of **cancers of the urinary tract**, and we found little evidence of a protective effect of paracetamol against ovarian cancer. The elevated risks for cancers of the esophagus, lung and liver are most likely a result of confounding variables, but may warrant further investigation.

2.8 Kato, I., K. L. Koenig, et al. (2002). "Use of anti-inflammatory and non-narcotic analgesic drugs and risk of non-Hodgkin's lymphoma (NHL) (United States)."

Cancer Causes Control 13(10): 965-974.

OBJECTIVE: To examine whether exposures to anti-inflammatory and non-narcotic analgesic drugs are associated with risk of **non-Hodgkin's lymphoma (NHL)**. METHODS: A case-control study was conducted among women living in upstate New York. The study involved 376 cases of NHL identified through the New York State Cancer Registry and 463 controls randomly selected from the Medicare beneficiary files and New York State driver's license records. Information regarding use of common medications in the

past 20 years and potential confounding variables was obtained by telephone interview. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using an unconditional logistic regression model. RESULTS: There were non-significant increases in risk associated with ever use of cortisone injections and oral cortisone (OR = 1.44 (CI 0.98-2.11) for injections and 1.21 (CI 0.73-2.00) for oral cortisone, although there was no clear dose-response relationship with either type. On the other hand, the risk of **NHL** progressively increased with the frequency of use of non-steroidal anti-inflammatory and non-narcotic analgesic drugs (NSAID/NNAD) (p-value for trend 0.008). Women who used any of these medications daily for more than 10 years had an OR of 1.90 (CI 1.01-3.57), compared with those who used it less than once a month on average. The risk associated with long-term use was most pronounced for ibuprofen, intermediate for aspirin, and least for **acetaminophen**. CONCLUSIONS: Because the population-attributable risk associated with NSAID/NNAD use is potentially large, our results need to be verified in further epidemiologic studies.

2.9 Meier, C. R., S. Schmitz, et al. (2002). "Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer."

Pharmacotherapy 22(3): 303-309.

STUDY OBJECTIVE: To explore the association between exposure to acetaminophen (paracetamol) or nonsteroidal antiinflammatory drugs (NSAIDs) and risk of developing ovarian, breast, or colon cancer. DESIGN: Retrospective case-control study SETTING: General practice offices. SUBJECTS: Four hundred eighty-three women with ovarian cancer and 1877 women matched for age, years of medical history in computer record, general practice attended, and calendar time; 3706 women with breast cancer and 14,155 matched control subjects; and 635 women with colon cancer and 2434 matched control subjects. INTERVENTION: United Kingdom-based General Practice Research Database was searched for women aged 50-89 years with a first-time diagnosis of ovarian, breast, or colon cancer and for matched controls to assess prescription analgesic exposure. MEASUREMENTS AND MAIN RESULTS: Regular **acetaminophen** exposure (> or = 30 prescriptions) was associated with a slightly decreased risk of developing **breast** (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.7-1.0) but not **ovarian** (OR 1.0, 95% CI 0.6-1.5) or **colon** (OR 1.0, 95% CI 0.7-1.4) cancer. Regular NSAID exposure was associated with a reduced risk of colon (OR 0.5, 95% CI 0.3-0.9) but not ovarian or breast cancer. CONCLUSION: We found no evidence for a decreased ovarian cancer risk for women with regular acetaminophen or NSAID exposure.

2.10 Harris, R. E., R. T. Chlebowski, et al. (2003). "Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative."

Cancer Res 63(18): 6096-6101.

We analyzed data from the prospective Women's Health Initiative (WHI) Observational Study to examine the effects of regular use of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) on breast cancer risk. We studied a population of 80,741 postmenopausal women between 50 and 79 years of age who reported no history of breast cancer or other cancers (excluding nonmelanoma skin cancer), and we completed a personal baseline interview that elicited comprehensive health information including data on breast cancer risk factors and NSAID use. All of the cases were adjudicated by WHI physicians using pathology reports. Our analysis was based on 1392 confirmed cases of breast cancer. Relative risks (RRs) with 95% confidence intervals (CIs) were estimated with adjustment for age and other breast cancer risk factors. Regular NSAID use (two or more tablets/week) for 5-9 years produced a 21% reduction in the incidence of breast cancer (RR, 0.79; 95% CI, 0.60-1.04); regular NSAID use for 10 or more years produced a 28% reduction (RR, 0.72; CI, 0.56-0.91), and there was a statistically significant inverse linear trend of breast cancer incidence with the duration of NSAID use (P < 0.01). The estimated risk reduction for long-term use of ibuprofen (RR, 0.51; CI, 0.28-0.96) was greater than for aspirin (RR, 0.79; CI, 0.60-1.03). Subgroup analysis by breast cancer risk factors did not result in effect modification. Regular use of **acetaminophen** (an analgesic agent with little or no anti-inflammatory activity) or low-dose aspirin (<100 mg) was unrelated to the incidence of **breast cancer**. Our results indicate that the regular use of aspirin, ibuprofen, or other NSAIDs may have a significant chemopreventive effect against the development of breast cancer and underscore the need for clinical trials to confirm this effect.

2.11 Chang, E. T., T. Zheng, et al. (2004). "Aspirin and the risk of Hodgkin's lymphoma in a population-based case-control study."

J Natl Cancer Inst 96(4): 305-315.

BACKGROUND: Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased risk of several malignancies. NSAIDs may prevent cancer development by blocking the cyclooxygenase-catalyzed synthesis of proinflammatory prostaglandins. Aspirin may also protect against Hodgkin's lymphoma by inhibiting transcription factor nuclear factor kappaB (NF-kappaB), which is necessary for immune function and the survival of Hodgkin's lymphoma cells. We examined the association between regular analgesic use and the risk of Hodgkin's lymphoma. METHODS: A population-based case-control study of 565 case patients with Hodgkin's lymphoma and 679 control subjects was conducted in the metropolitan area of Boston, Massachusetts, and in the state of Connecticut. Participants reported their average use of aspirin,

non-aspirin NSAIDs, and acetaminophen over the previous 5 years. Regular analgesic use was defined as consumption of at least two tablets per week on average over the preceding 5 years; non-regular use was defined as consumption of fewer than two tablets per week. RESULTS: The risk of **Hodgkin's lymphoma** associated with regular aspirin use was statistically significantly lower (odds ratio [OR] = 0.60, 95% confidence interval [CI] = 0.42 to 0.85) than that associated with non-regular aspirin use. The risk was not associated with use of other non-aspirin NSAIDs (OR = 0.97, 95% CI = 0.73 to 1.30). However, the risk associated with regular **acetaminophen** use was statistically significantly higher (OR = 1.72, 95% CI = 1.29 to 2.31) than that associated with non-regular use. CONCLUSION: The inverse association between aspirin, but not other NSAIDs, and Hodgkin's lymphoma suggests that NF-kappaB signaling may play a key role in Hodgkin's lymphoma pathogenesis.

2.12 Garcia Rodriguez, L. A. and A. Gonzalez-Perez (2004a). "Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer."

Cancer Epidemiol Biomarkers Prev 13(4): 649-653.

BACKGROUND: Prostate cancer is considered a major health problem in western countries. Promising results from observational studies on cancer at other sites fuelled the publication of several studies assessing the association between nonsteroidal anti-inflammatory drug (NSAID) use and prostate cancer. However, these studies show conflicting results. METHODS: We conducted a cohort study with a nested case-control analysis to further study the association between NSAIDs and **prostate cancer**. We used data from the General Practice Research Database in United Kingdom. RESULTS: Aspirin use was associated with a reduced risk of prostate cancer [odds ratio (OR) = 0.70, 95% confidence interval (95% CI) = 0.61-0.79]. We also found that **paracetamol** use with a treatment duration longer than 1 year was associated with a decreased risk (OR = 0.65, 95% CI = 0.54-0.78). Non-aspirin-NSAID (NA-NSAID) and **paracetamol** short-term use was associated with a small increased risk whereas long-term users of NA-NSAIDs presented an OR of 0.89 (95% CI = 0.73-1.08). DISCUSSION: Our findings support a protective effect of aspirin and paracetamol against prostate cancer. The transient elevated risk observed among newly started users of NA-NSAIDs and paracetamol is most likely explained by prothopathic bias. We found some suggestion of a reduced risk with long-term use of NA-NSAID.

2.13 Garcia Rodriguez, L. A. and A. Gonzalez-Perez (2004b). "Risk of breast cancer among users of aspirin and other anti-inflammatory drugs."

Br J Cancer 91(3): 525-529.

We conducted a cohort study with a nested case-control analysis to evaluate the effect of anti-inflammatory drugs in breast cancer incidence using the General Practice Research Database. Women taking aspirin and paracetamol for 1 year or longer had an odds ratio (OR) of 0.77 (95 percent confidence interval (95% CI): 0.62,0.95) and 0.76 (95% CI: 0.65,0.88), respectively, compared to nonusers. Daily doses of aspirin (75 mg) and paracetamol (up to 2000 mg) showed the greatest reduced risk. Use of non-aspirin nonsteroidal anti-inflammatory drugs for more than 1 year was not associated with a reduced risk of breast cancer (OR=1.00 (95% CI: 0.84, 1.17), and the corresponding estimate among users with at least 2 years duration was similar. Our findings suggest that aspirin at cardioprophylactic doses as well as **paracetamol** at analgesic doses is associated with a reduced risk of **breast cancer.**

2.14 Sivak-Sears, N. R., J. A. Schwartzbaum, et al. (2004). "Case-control study of use of nonsteroidal antiinflammatory drugs and glioblastoma multiforme."

Am J Epidemiol 159(12): 1131-1139.

Evidence from epidemiologic and experimental studies suggests that use of nonsteroidal antiinflammatory drugs (NSAIDs) reduces risk of colon and breast cancer. The association between use of aspirin and other NSAIDs and risk of adult **glioblastoma multiforme (GBM)** was evaluated among 236 incident GBM cases and 401 population-based controls frequency-matched on age, gender, and ethnicity from the San Francisco Bay Area Adult Glioma Study. Cases (or proxies) and controls were interviewed in person between May 1997 and August 2000. Cases with self-reported GBM reported less use of at least 600 pills of all types of NSAIDs combined during the 10-year prediagnostic period than did controls (odds ratio (OR) = 0.53, 95% confidence interval (CI): 0.3, 0.8). Findings were consistent for aspirin (OR = 0.51, 95% CI: 0.3, 0.8), ibuprofen (OR = 0.41, 95% CI: 0.2, 0.8), and naproxen/other NSAIDs (OR = 0.34, 95% CI: 0.1, 0.8). **GBM** cases also reported less use of **acetaminophen** than did controls (OR = 0.51, 95% CI: 0.3, 1.0). Eliminating participants who initiated NSAID use within 2 years of diagnosis yielded similar results. These findings show an inverse association between NSAID use and GBM. Further studies are warranted to determine whether NSAIDs might be effective in the inhibition of GBM development or progression.

2.15 Terry, M. B., M. D. Gammon, et al. (2004). "Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk."

JAMA 291(20): 2433-2440.

CONTEXT: Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a decrease in the risk of several cancers,

including breast cancer. NSAIDs inhibit cyclooxygenase activity and thereby reduce prostaglandin synthesis; prostaglandins stimulate aromatase gene expression and thereby stimulate estrogen biosynthesis. Given the importance of estrogen in the pathogenesis of breast cancer, the ability of aspirin and other NSAIDs to protect against breast cancer could vary according to hormone receptor status. OBJECTIVES: To determine the association between the frequency and duration of use of aspirin and other NSAIDs and breast cancer risk and to investigate whether any observed association is more pronounced for women with hormone receptor-positive breast cancers. DESIGN, SETTING, AND PATIENTS: Population-based case-control study of women with breast cancer, including in-person interviews conducted on Long Island, NY, during 1996-1997 (1442 cases and 1420 controls). MAIN OUTCOME MEASURE: Incident invasive and in situ breast cancer by aspirin and NSAID use and hormone receptor status. RESULTS: Ever use of aspirin or other NSAIDs at least once per week for 6 months or longer was reported in 301 cases (20.9%) and 345 controls (24.3%) (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.66-0.97 for ever vs nonusers). The inverse association was most pronounced among frequent users (> or =7 tablets per week) (OR, 0.72; 95% CI, 0.58-0.90). The results for ibuprofen, which was used by fewer women on a regular basis, were generally weaker (OR, 0.78; 95% CI, 0.55-1.10 for <3 times per week vs OR, 0.92; 95% CI, 0.70-1.22 for > or =3 times per week). Use of **acetaminophen**, an analgesic that does not inhibit prostaglandin synthesis, was not associated with a reduction in the incidence of **breast cancer**. The reduction in risk with aspirin use was seen among those with hormone receptor-positive tumors (OR, 0.74; 95% CI, 0.60-0.93) but not for women with hormone receptor-negative tumors (OR, 0.97; 95% CI, 0.67-1.40). CONCLUSION: These data add to the growing evidence that supports the regular use of aspirin and other NSAIDs (which may operate through inhibition of estrogen biosynthesis) as effective chemopreventive agents for breast cancer.

2.16 Baker, J. A., J. R. Weiss, et al. (2005). "Regular use of aspirin or acetaminophen and risk of non-Hodgkin lymphoma."

Cancer Causes Control 16(3): 301-308.

Regular use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been hypothesized to be associated with reduced risk of **non-Hodgkin lymphoma (NHL)**, although previous results have been inconsistent. The current study investigated the effects of regular aspirin or acetaminophen use on non-Hodgkin lymphoma risk among 625 individuals with primary, incident NHL and 2512 age and sex matched hospital controls with non-neoplastic conditions who completed a comprehensive epidemiologic questionnaire. Results indicate that regular aspirin use may be associated with decreased NHL risk among men [adjusted odds ratio (aOR) 0.82, 95% confidence interval (CI), 0.65--1.04], but not among women (aOR 0.93, 95% CI, 0.71--1.23). In contrast, regular **acetaminophen** use was associated with elevated **NHL** risk among women

(aOR 1.71, 95% CI, 1.18--2.50) but not among men (aOR 0.75, 95% CI, 0.48--1.17). Other studies have demonstrated that acetaminophen is associated with transient decreases in DNA repair, and lymphocytes may be particularly susceptible to DNA damage, suggesting a mechanism for the elevated NHL risk observed.

2.17 Moysich, K. B., J. A. Baker, et al. (2005). "Regular analgesic use and risk of endometrial cancer."

Cancer Epidemiol Biomarkers Prev 14(12): 2923-2928.

BACKGROUND: Analgesic use has been implicated in the chemoprevention of a number of solid tumors, but thus far, no previous research has focused on the role of aspirin in endometrial cancer etiology.METHODS: We conducted a hospital-based case-control study of 427 women with primary, incident endometrial cancer, and 427 age- and residence-matched controls without benign or malignant neoplasms. All participants received medical services at Roswell Park Cancer Institute in Buffalo, NY, and completed a comprehensive epidemiologic questionnaire. Women who reported analgesic use at least once a week for at least 6 months were classified as regular users and served as the reference group throughout the analyses. We used unconditional logistic regression analyses to compute crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI).RESULTS: Compared with nonusers, regular aspirin users were not at reduced risk of **endometrial cancer** (adjusted OR, 0.91; 95% CI, 0.66-1.26), nor were women with the highest frequency, duration, or cumulative lifetime aspirin use. When the sample was divided by body mass index status, regular aspirin use was not associated with risk among women classified as normal weight or overweight, but a significant risk reduction was seen for obese women (adjusted OR, 0.50; 95% CI, 0.27-0.92). Significant decreases in risk were also observed for obese women with the greatest frequency, duration, and cumulative aspirin use. No significant associations in the overall sample or among obese women were noted for **acetaminophen** use.CONCLUSION: We observed no evidence of an overall chemoprotective effect of aspirin on endometrial cancer risk, but the significant risk reductions among obese women warrant further investigation.

2.18 Fortuny, J., M. Kogevinas, et al. (2006). "Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain."

Cancer Epidemiol Biomarkers Prev 15(9): 1696-1702.

BACKGROUND: We assessed use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAID), aspirin, paracetamol (acetaminophen), phenacetin, and metamizol (dipyrone) and risk of bladder cancer and their interaction with polymorphisms in drug-metabolizing genes. METHODS: We analyzed personal interview data from 958 incident bladder cancer cases and 1,029 hospital

controls from a multicenter case-control study in Spain. A drug matrix was developed to estimate cumulative lifetime dose of active ingredients. Polymorphisms in GSTP1, SULT1A1, CYP2E1, CYP2C9, and NAT2 were examined. RESULTS: A significant reduction in bladder cancer risk [adjusted odds ratio (OR), 0.4; 95% confidence interval (95% CI), 0.2-0.9] was observed for regular users of nonaspirin NSAIDs compared with never users. Regular users of aspirin experienced no reduction in risk (OR, 1.0; 95% CI, 0.7-1.5). Regular users of **paracetamol** had no overall increased risk of **bladder cancer** (OR, 0.8; 95% CI, 0.4-1.3), but our data suggested a qualitative interaction with the GSTP1 I105V genotype. Subjects with at least one copy of the 359L or 144C variant alleles in the NSAID-metabolizing gene CYP2C9 had a slightly decreased risk of bladder cancer (OR, 0.8; 95% CI, 0.7-1.0; P = 0.037); however, having at least one copy of the 359L or 144C variant alleles did not significantly modify the protective effect of nonaspirin NSAID use. CONCLUSION: Regular use of nonaspirin NSAIDs was associated with a reduced risk of bladder cancer, which was not modified by polymorphisms in the NSAID-metabolizing gene CYP2C9. We found no evidence of an overall effect for paracetamol or aspirin use.

2.19 Harris, R. E., J. Beebe-Donk, et al. (2006). "Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors."

BMC Cancer 6: 27.

BACKGROUND: Epidemiologic and laboratory investigations suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) have chemopreventive effects against breast cancer due to their activity against cyclooxygenase-2 (COX-2), the rate-limiting enzyme of the prostaglandin cascade. METHODS: We conducted a case control study of breast cancer designed to compare effects of selective and non-selective COX-2 inhibitors. A total of 323 incident breast cancer patients were ascertained from the James Cancer Hospital, Columbus, Ohio, during 2003-2004 and compared with 649 cancer free controls matched to the cases at a 2:1 ratio on age, race, and county of residence. Data on the past and current use of prescription and over the counter medications and breast cancer risk factors were ascertained using a standardized risk factor questionnaire. Effects of COX-2 inhibiting agents were quantified by calculating odds ratios (OR) and 95% confidence intervals. RESULTS: Results showed significant risk reductions for selective COX-2 inhibitors as a group (OR = 0.29, 95% CI = 0.14-0.59), regular aspirin (OR = 0.49, 95% CI = 0.26-0.94), and ibuprofen or naproxen (0.36, 95% CI = 0.18-0.72). **Acetaminophen**, a compound with negligible COX-2 activity and low dose aspirin (81 mg) produced no significant change in the risk of **breast cancer**. CONCLUSION: Selective COX-2 inhibitors (celecoxib and rofecoxib) were only recently approved for use in 1999, and rofecoxib (Vioxx) was withdrawn from the marketplace in 2004. Nevertheless, even in the short window of exposure to these compounds, the selective COX-2 inhibitors

produced a significant (71%) reduction in the risk of breast cancer, underscoring their strong potential for breast cancer chemoprevention.

2.20 Schildkraut, J. M., P. G. Moorman, et al. (2006). "Analgesic drug use and risk of ovarian cancer."

Epidemiology 17(1): 104-107.

BACKGROUND: Previous epidemiologic research suggests that analgesic use may reduce the risk of ovarian cancer, although results are not consistent. METHODS: In a population-based, case-control study, we analyzed data from 586 ovarian cancer cases and 627 matched controls in North Carolina for the relationship between analgesic use and ovarian cancer risk. Logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) while adjusting for potential confounders. RESULTS: Use of any nonsteroidal antiinflammatory drugs, including aspirin, within 5 years of diagnosis/interview was found to be associated with a reduction in the risk of **ovarian cancer** (adjusted OR = 0.72; 95% CI = 0.56-0.92). For use of **acetaminophen**, the OR was 0.78 (95% CI = 0.56-1.08). CONCLUSIONS: These data support an inverse relationship between the use of both nonsteroidal antiinflammatory drugs and acetaminophen and the risk of ovarian cancer.

2.21 Weiss, J. R., J. A. Baker, et al. (2006). "Opposing effects of aspirin and acetaminophen use on risk of adult acute leukemia."

Leuk Res 30(2): 164-169.

Regular use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been hypothesized to be associated with reduced risk of hematologic cancer, although previous results have been inconsistent. The current study investigated the effects of aspirin or acetaminophen use on adult acute leukemia risk among 169 individuals with leukemia and 676 age and sex matched hospital controls with non-neoplastic conditions who completed a comprehensive epidemiologic questionnaire. Results indicate that regular aspirin use may be associated with a modest decrease in leukemia risk [adjusted odds ratio (aOR), 0.84; 95% confidence interval (CI), 0.59-1.21]. In contrast, ever using **acetaminophen** was associated with elevated **leukemia** risk (aOR, 1.53; 95% CI, 1.03-2.26). Results did not differ between men and women. Other studies have demonstrated that acetaminophen is associated with transient decreases in DNA repair, and lymphocytes may be particularly susceptible to DNA damage, suggesting a mechanism for the elevated acute leukemia risk observed among acetaminophen users.

2.22 Fortuny, J., M. Kogevinas, et al. (2007). "Analgesic and anti-inflammatory drug use and risk of bladder cancer: a population based case control study."

BMC Urol 7: 13.

BACKGROUND: Use of phenacetin and other analgesic and non-steroidal anti-inflammatory drugs (NSAIDs) potentially influences bladder cancer incidence, but epidemiologic evidence is limited. METHODS: We analyzed data from 376 incident bladder cancer cases and 463 controls from a population-based case-control study in New Hampshire on whom regular use of analgesic drugs and NSAIDs was obtained. Odds ratios and 95% confidence intervals were computed using logistic regression with adjustment for potentially confounding factors. Separate models by tumor stage, grade and TP53 status were conducted. RESULTS: We found an elevated odds ratio (OR) associated with reported use of phenacetin-containing medications, especially with longer duration of use (OR >8 years = 3.00, 95% confidence interval (CI) = 1.4-6.5). In contrast, use of **paracetamol** did not relate overall to risk of **bladder cancer**. We also found that regular use of any NSAID was associated with a statistically significant decrease in bladder cancer risk (OR = 0.6, 95% CI = 0.4-0.9), and specifically use of aspirin. Further, the association with NSAID use was largely among invasive, high grade and TP53 positive tumors. CONCLUSION: While these agents have been investigated in several studies, a number of questions remain regarding the effects of analgesic and NSAID use on risk of bladder cancer.

2.23 Genkinger, J. M., I. De Vivo, et al. (2007). "Nonsteroidal antiinflammatory drug use and risk of bladder cancer in the health professionals follow-up study."

Int J Cancer 120(10): 2221-2225.

Nonsteroidal antiinflammatory drugs (NSAIDs) use, particularly aspirin, may lower the risk of several cancers, including bladder. NSAIDs may reduce development of bladder tumors by decreasing inflammation, inhibiting cycloxygenase-2, inhibiting proliferation and inducing apoptosis of cancer cells. However, acetaminophen, a major metabolite of phenacetin, may be positively associated with bladder cancer risk. Results from case-control studies on NSAIDs and acetaminophen use and bladder cancer risk are inconsistent. We investigated the association between NSAID and acetaminophen use and bladder cancer risk in a large cohort of US males. Among 49,448 men in the Health Professionals Follow-Up Study, 607 **bladder cancer** cases were confirmed during 18 years of follow-up. Relative risks (RR) and 95% confidence intervals (CI) were calculated by Cox proportional hazards models. Multivariate RR were adjusted for age, current smoking status, pack years, geographic region and fluid intake. No significant associations were observed for regular aspirin (> or =2 tablets per week), (RR = 0.99, 95% CI 0.83-1.18), ibuprofen (RR = 1.11, 95% CI 0.81-1.54), **acetaminophen** (RR = 0.96, 95% CI 0.67-1.39) or total NSAID use (not including acetaminophen; RR = 1.01, 95% CI 0.85-1.20) and bladder cancer risk compared with nonuse. Consistent use (over 6 years) of aspirin, ibuprofen, acetaminophen and total NSAIDs, compared to nonuse, was not associated with bladder cancer risk. No association was observed between

aspirin frequency and dose and bladder cancer risk. We observed no effect-modification by smoking, age or fluid intake. Our results suggest that regular NSAID or acetaminophen use has no substantial impact on bladder cancer risk among men.

2.24 Harris, R. E., J. Beebe-Donk, et al. (2007). "Reduced risk of human lung cancer by selective cyclooxygenase 2 (COX-2) blockade: results of a case control study."

Int J Biol Sci 3(5): 328-334.

We conducted a case control study of selective cyclooxygenase-2 (COX-2) blocking agents and lung cancer. A total of 492 newly diagnosed lung cancer cases were ascertained during January 1, 2002 to September 30, 2004, at The Ohio State University Medical Center, Columbus, Ohio. All cases were confirmed by examination of the pathology report. Healthy population controls without cancer were ascertained during the same time period. Controls were frequency matched at a rate of 2:1 to the cases by age, gender, and county of residence. We collected information on type, frequency, and duration of use of selective COX-2 inhibitors (primarily celecoxib or rofecoxib) and nonselective NSAIDs such as ibuprofen and aspirin. Estimates of odds ratios (OR) were obtained with adjustment for cigarette smoking, age and other potential confounders using logistic regression analysis. Odds Ratios for selective COX-2 inhibitors were adjusted for past use of other NSAIDs. Use of any selective COX-2 inhibitor for more than one year produced a significant (60%) reduction in the risk of **lung cancer** (OR=0.40, 95% CI=0.19-0.81). Observed risk reductions were consistent for men (OR=0.26, 95% CI=0.10-0.62) and women (OR=0.52, 95% CI=0.24-1.13) and for individual COX-2 inhibitors (OR=0.28, 95% CI=-0.12-0.67, for celecoxib and OR=0.55, 95% CI=0.19-1.56, for rofecoxib). Intake of ibuprofen or aspirin also produced significant risk reductions (OR=0.40, 95% CI=0.23-0.73 and OR=0.53, 95% CI=0.34-0.82, respectively), whereas **acetaminophen**, an analgesic with negligible COX-2 activity, had no effect on the risk (OR=1.36, 95% CI=0.53-3.37). This investigation demonstrates for the first time that selective COX-2 blocking agents have strong potential for the chemoprevention of human lung cancer.

2.25 Kwan, M. L., L. A. Habel, et al. (2007). "NSAIDs and breast cancer recurrence in a prospective cohort study."

Cancer Causes Control 18(6): 613-620.

OBJECTIVE: We examined the association between NSAID use and breast cancer recurrence in a prospective cohort of 2,292 early-stage breast cancer survivors diagnosed from 1997 to 2000 participating in the Life After Cancer Epidemiology (LACE) Study. METHODS: From 2000 to 2002, mailed questionnaires were used to obtain information on aspirin, ibuprofen, and other NSAID use and subsequent breast cancer events. A total of 270 recurrences

(local, regional, and distant disease and new primary breast cancers) were reported and verified by medical record review. Cox proportional hazard models were used to estimate rate ratios (RR) and 95% confidence intervals (CI), adjusting for age at diagnosis, race, cancer stage, tamoxifen treatment, chemotherapy use, body mass index, and cyclooxygenase-2 (COX2) inhibitor use. RESULTS: Current, regular use (at least three days per week at time of questionnaire administration) of ibuprofen (RR, 0.56; 95% CI, 0.32-0.98), but not aspirin (RR, 1.09; 95% CI, 0.74-1.61), was associated with a statistically significant decreased risk of **breast cancer recurrence**. The combination of ibuprofen and other non-aspirin NSAIDs such as naproxen and sulindac reflected a similar reduction in risk (RR, 0.56; 95% CI, 0.33-0.95). No association was found for the non-NSAID analgesic **acetaminophen**. CONCLUSION: Our findings provide support for an inverse association between current, regular ibuprofen use and breast cancer recurrence.

2.26 Moysich, K. B., M. R. Bonner, et al. (2007). "Regular analgesic use and risk of multiple myeloma."

Leuk Res 31(4): 547-551.

Analgesic use has been implicated in the chemoprevention of a number of solid tumors, but to date no previous research has focused on the role of analgesics in the etiology of **multiple myeloma (MM)**. We conducted a hospital-based case-control study of 117 patients with primary, incident MM and 483 age and residence matched controls without benign or malignant neoplasms. All participants received medical services at Roswell Park Cancer Institute in Buffalo, NY, and completed a comprehensive epidemiological questionnaire. Participants who reported analgesic use at least once a week for at least 6 months were classified as regular users; individuals who did not use analgesics regularly served as the reference group throughout the analyses. We used unconditional logistic regression analyses to compute crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Compared to non-users, regular aspirin users were not at reduced risk of **MM** (adjusted OR=0.99; 95% CI 0.65-1.49), nor were participants with the highest frequency or duration of aspirin use. A significant risk elevation was found for participants who were regular **acetaminophen** users (adjusted OR=2.95; 95% CI 1.72-5.08). Further, marked increases in risk of MM were noted with both greater frequency (>7 tablets weekly; adjusted OR=4.36; 95% CI 1.70-11.2) and greater duration (>10 years; adjusted OR=3.26; 95% CI 1.52-7.02) of acetaminophen use. We observed no evidence of a chemoprotective effect of aspirin on MM risk, but observed significant risk elevations with various measures of acetaminophen use. Our results warrant further investigation in population-based case-control and cohort studies and should be interpreted with caution in light of the limited sample size and biases inherent in hospital-based studies.

2.27 Friis, S., L. Thomassen, et al. (2008). "Nonsteroidal anti-inflammatory drug use and breast cancer risk: a Danish cohort study."

Eur J Cancer Prev 17(2): 88-96.

Epidemiologic studies investigating the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on breast cancer have yielded conflicting results. We examined the association between use of aspirin and nonaspirin NSAIDs and breast cancer risk among 28 695 women in the Danish Diet, Cancer and Health cohort. Information on NSAID and paracetamol use was obtained from a self-administered questionnaire completed at baseline (1993-1997) and updated through 2003 using a nationwide prescription database. Detailed information on breast cancer incidence and tumour characteristics was obtained from nationwide health registers. Cox proportional hazards regression was used to compute incidence rate ratios (RRs) and 95% confidence intervals (CIs). We identified 847 breast cancer cases over an average follow-up period of 7.5 years. Any NSAID use at baseline was associated with an increased incidence of breast cancer compared with nonuse (RR, 1.27; 95% CI, 1.10-1.45). A similar result was observed for any NSAID use in a combined analysis of baseline and prescription data (1.34; 95% CI, 1.15-1.56). Aspirin-only users experienced a slightly higher breast cancer incidence (RR, 1.38; 95% CI, 1.12-1.69) than exclusive users of nonaspirin NSAIDs (RR, 1.25; 95% CI, 1.04-1.49). Introduction of a lag time of 1 year provided similar results. We found no clear differences in risk estimates with frequency, recency or duration of NSAID use, or by hormone receptor status of the breast tumours. **Paracetamol** use was unrelated to **breast cancer** incidence. The increased breast cancer incidence among NSAID users may reflect a noncausal association, but our study provides no evidence of a chemopreventive effect of NSAIDs against breast cancer over the durations studied.

2.28 Hannibal, C. G., M. A. Rossing, et al. (2008). "Analgesic drug use and risk of epithelial ovarian cancer."

Am J Epidemiol 167(12): 1430-1437.

Analgesic use may reduce ovarian cancer risk, possibly through antiinflammatory or antigonadotropic effects. The authors conducted a population-based, case-control study in Washington State that included 812 women aged 35-74 years who were diagnosed with epithelial ovarian cancer between 2002 and 2005 and 1,313 controls. Use of analgesics, excluding use within the previous year, was assessed via in-person interviews. Logistic regression was used to calculate odds ratios and 95% confidence intervals. Overall, **acetaminophen** and aspirin were associated with weakly increased risks of **ovarian cancer**. These associations were stronger after more than 10 years of use (acetaminophen: odds ratio (OR) = 1.8, 95% confidence interval (CI): 1.3, 2.6; aspirin: OR = 1.6, 95% CI: 1.1, 2.2) and were present for

indications of headache, menstrual pain, and other pain/injury. Reduced risk was observed among aspirin users who began regular use within the previous 5 years (OR = 0.6, 95% CI: 0.4, 1.0) or used this drug for prevention of heart disease (OR = 0.7, 95% CI: 0.5, 1.0). These results, in the context of prior findings, do not provide compelling evidence of a true increase in risk of ovarian cancer among women who use these drugs. However, they add to the weight of evidence that, in the aggregate, provides little support for the use of analgesic drugs as chemoprevention for this disease.

2.29 Harris, R. E., J. Beebe-Donk, et al. (2008). "Similar reductions in the risk of human colon cancer by selective and nonselective cyclooxygenase-2 (COX-2) inhibitors."

BMC Cancer 8: 237.

BACKGROUND: Epidemiologic and laboratory investigations suggest that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have chemopreventive effects against colon cancer perhaps due at least in part to their activity against cyclooxygenase-2 (COX-2), the rate-limiting enzyme of the prostaglandin cascade. METHODS: We conducted a case control study of colon cancer designed to compare effects of selective and non-selective COX-2 inhibitors. A total of 326 incident colon cancer patients were ascertained from the James Cancer Hospital, Columbus, Ohio, during 2003-2004 and compared with 652 controls with no history of cancer and matched to the cases at a 2:1 ratio on age, race, and county of residence. Data on the past and current use of prescription and over the counter medications and colon cancer risk factors were ascertained using a standardized risk factor questionnaire. Effects of COX-2 inhibiting agents were quantified by calculating odds ratios (OR) and 95% confidence intervals. RESULTS: Results showed significant risk reductions for selective COX-2 inhibitors (OR = 0.31, 95% CI = 0.16-0.57), regular aspirin (OR = 0.33, 95% CI = 0.20-0.56), and ibuprofen or naproxen (0.28, 95% CI = 0.15-0.54). **Acetaminophen**, a compound with negligible COX-2 activity and low dose aspirin (81 mg) produced no significant change in the risk of **colon cancer**. CONCLUSION: These results suggest that both non-selective and selective COX-2 inhibitors produce significant reductions in the risk of colon cancer, underscoring their strong potential for colon cancer chemoprevention.

2.30 Sadeghi, S., C. J. Bain, et al. (2008). "Aspirin, nonsteroidal anti-inflammatory drugs, and the risks of cancers of the esophagus."

Cancer Epidemiol Biomarkers Prev 17(5): 1169-1178.

BACKGROUND: Frequent consumption of aspirin and nonsteroidal anti-inflammatory drugs (NSAID) has been associated with reduced occurrence of cancers of the esophagus, although potential modifying effects of other causal factors remain relatively unexplored. METHODS: We compared nationwide samples of Australian patients with adenocarcinomas of the esophagus (EAC; n

= 367) or esophagogastric junction (EGJAC; n = 426) or esophageal squamous cell carcinoma (ESCC; n = 309) with control participants sampled from a population register (n = 1,580). Intakes of aspirin, other NSAIDs, and acetaminophen (paracetamol) were assessed from self-reports. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) using multivariable logistic regression. RESULTS: Compared with never-users of aspirin, those who used aspirin at least weekly had significantly lower risks of EAC (OR, 0.48; 95% CI, 0.32-0.72), EGJAC (OR, 0.71; 95% CI, 0.49-1.01), and ESCC (OR, 0.63; 95% CI, 0.40-0.98). At least weekly use of other NSAIDs was also associated with reduced risks of EAC (OR, 0.74; 95% CI, 0.51-1.08), EGJAC (OR, 0.53; 95% CI, 0.37-0.77), and ESCC (OR, 0.46; 95% CI, 0.30-0.73). No association was observed between frequent use of **acetaminophen** and **esophageal cancer**. Risk reductions for EAC among users of aspirin and NSAIDs were greater among those who experienced at least weekly symptoms of reflux (OR, 0.26; 95% CI, 0.12-0.55 and OR, 0.41; 95% CI, 0.21-0.77, respectively) than those who did not experience reflux (OR, 0.96; 95% CI, 0.46-2.00 and OR, 0.78; 95% CI, 0.35-1.72, respectively). Recent use of NSAIDs in the past 5 years was associated with greater risk reductions. CONCLUSIONS: Frequent use of aspirin and NSAIDs is associated with reduced occurrence of esophageal cancers, particularly among those with frequent symptoms of gastroesophageal reflux.

2.31 Viswanathan, A. N., D. Feskanich, et al. (2008). "Aspirin, NSAID, and acetaminophen use and the risk of endometrial cancer."

Cancer Res 68(7): 2507-2513.

To date, no prospective studies have explored the relationship between the use of aspirin, other nonsteroidal anti-inflammatory medications (NSAID), and acetaminophen and endometrial adenocarcinoma. Of the 82,971 women enrolled in a prospective cohort study, 747 developed medical record-confirmed invasive endometrial cancer over a 24-year period. Use of aspirin was ascertained from 1980 to 2004, and for other NSAIDs and acetaminophen, from 1990 to 2004. Cox regression models calculated multivariate relative risks (MV RR), controlling for body mass index (BMI), postmenopausal hormone (PMH) use, and other endometrial cancer risk factors. Currency, duration, and quantity of aspirin were not associated with endometrial cancer risk overall [current use: MV RR, 1.03; 95% confidence interval (CI) 0.83-1.27; >10 years of use: MV RR, 1.01; 95% CI, 0.78-1.30; and cumulative average >7 tablets per week: (MV RR, 1.10; 95% CI, 0.84-1.44)]. However, stratified analyses showed that a lower risk of endometrial cancer among obese (BMI, >or=30 kg/m(2)) women was seen with current aspirin use (MV RR, 0.66; 95% CI, 0.46-0.95). The greatest risk reduction for current aspirin users was seen in postmenopausal obese women who had never used PMH (MV RR, 0.43; 95% CI, 0.26-0.73). The use of other NSAIDs or **acetaminophen** was not associated with **endometrial cancer**. Our data suggest that use of aspirin or other NSAIDs does not play an important role in endometrial cancer risk overall. However, risk was significantly lower for current

aspirin users who were obese or who were postmenopausal and had never used PMHs; these subgroup findings require further confirmation.

2.32 Becker, N., J. Fortuny, et al. (2009). "Medical history and risk of lymphoma: results of a European case-control study (EPILYMPH)."

J Cancer Res Clin Oncol 135(8): 1099-1107.

INTRODUCTION: Lymphomas are a heterogeneous group of immune-cell malignancies. Immunology-related conditions are among the few factors for which consistent evidence exists relating them to lymphoma risk. MATERIALS AND METHODS: We used the data from the European case-control study Epilymph on 2,362 **lymphoma** cases and 2,458 controls to investigate associations between a medical history of infectious and non-infectious diseases with overall and subentity-specific lymphoma risk. RESULTS: As key results, we observed an increased odds ratio (OR) for self-reported infections with hepatitis B virus (HBV, OR = 1.91, 95% CL = 1.24-2.94) and a null result for rheumatoid arthritis. Additionally, we found an increased OR for infectious mononucleosis (OR = 1.68, 95% CL = 1.14-2.48), an inverse association to frequency of sickness in childhood (OR = 0.68, 95% CL = 0.55-0.84), and-as casual finding-an increased OR with **acetaminophen** intake (OR = 2.29, 95% CL = 1.49-3.51). CONCLUSION: Our results are consistent with the current knowledge about the association with mononucleosis as indicator of Epstein-Barr-virus infection, suggest serological study of the association to HBV infection and do not support the view of a positive association between rheumatoid arthritis and lymphoma risk.

2.33 Eliassen, A. H., W. Y. Chen, et al. (2009). "Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and risk of breast cancer among premenopausal women in the Nurses' Health Study II."

Arch Intern Med 169(2): 115-121; discussion 121.

BACKGROUND: The use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is widespread for treatment of common symptoms such as headaches, muscular pain, and inflammation. In addition, the chemopreventive use of NSAIDs is increasingly common for heart disease and colon cancer. Evidence of a protective association with breast cancer risk has been inconsistent, and few data exist for premenopausal women. METHODS: We assessed the associations for use of aspirin, other NSAIDs, and acetaminophen with breast cancer risk among premenopausal women in the prospective Nurses' Health Study II. In total, 112,292 women, aged 25 to 42 years and free of cancer in 1989, were followed up until June 2003. Multivariate relative risks and 95% confidence intervals were calculated by Cox proportional hazards models, adjusting for age and other important breast cancer risk factors. RESULTS: Overall, 1345 cases of invasive premenopausal breast cancer were

documented. Regular use of aspirin (> or = 2 times per week) was not significantly associated with breast cancer risk (relative risk, 1.07; 95% confidence interval, 0.89-1.29). Regular use of either nonaspirin NSAIDs or **acetaminophen** also was not consistently associated with **breast cance**r risk. Results did not vary by frequency (days per week), dose (tablets per week), or duration of use. Furthermore, associations with each drug category did not vary substantially by estrogen and progesterone receptor status of the tumor. CONCLUSION: These data suggest that the use of aspirin, other NSAIDs, and acetaminophen is not associated with a reduced risk of breast cancer among premenopausal women.

2.34 Pinheiro, S. P., S. S. Tworoger, et al. (2009). "Use of nonsteroidal antiinflammatory agents and incidence of ovarian cancer in 2 large prospective cohorts."

Am J Epidemiol 169(11): 1378-1387.

Epidemiologic data on the association between nonsteroidal antiinflammatory drugs (NSAIDs) and ovarian cancer risk have been inconsistent. The authors prospectively examined the association between regular use of aspirin and nonaspirin NSAIDs and ovarian cancer incidence among 197,486 participants of the Nurses' Health Study (NHS) and the Nurses' Health Study-II (NHS-II) over 24 and 16 years of follow-up, respectively. Information on aspirin was initially assessed in 1980 (NHS) and 1989 (NHS-II) and on nonaspirin NSAIDs and acetaminophen in 1990 (NHS) and 1989 (NHS-II) and updated throughout follow-up. The authors used Cox proportional hazards models adjusting for **ovarian cancer** risk factors. A total of 666 confirmed cases of epithelial ovarian cancer were identified over 2,790,986 person-years of follow-up. The hazard ratios associated with regular use of aspirin, nonaspirin NSAIDs, and **acetaminophen** were 1.11 (95% confidence interval (CI): 0.92, 1.33), 0.81 (95% CI: 0.64, 1.01), and 1.14 (95% CI: 0.92, 1.43), respectively. The authors did not observe a dose-response relation with increased frequency or duration of regular use of any of these medications and ovarian cancer incidence. The results did not differ substantially by tumor histology. In this large prospective study, the authors found no compelling evidence to support an association between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer incidence.

2.35 Salinas, C. A., E. M. Kwon, et al. (2010). Use of aspirin and other nonsteroidal antiinflammatory medications in relation to prostate cancer risk.

Am J Epidemiol. United States. 172: 578-590.

Recent interest has focused on the role that inflammation may play in the development of prostate cancer and whether use of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) affects risk. In a population-based case-control

study designed to investigate the relation between these medications and prostate cancer risk, detailed exposure data were analyzed from 1,001 cases diagnosed with prostate cancer between January 1, 2002, and December 31, 2005, and 942 age-matched controls from King County, Washington. A significant 21% reduction in the risk of prostate cancer was observed among current users of aspirin compared with nonusers (95% confidence interval (CI): 0.65, 0.96). Long-term use of aspirin (>5 years: odds ratio = 0.76, 95% CI: 0.61, 0.96) and daily use of low-dose aspirin (odds ratio = 0.71, 95% CI: 0.56, 0.90) were also associated with decreased risk. There was no evidence that the association with aspirin use varied by disease aggressiveness, but there was effect modification (P(interaction) = 0.02) with a genetic variant in prostaglandin-endoperoxide synthase 2 (PTGS2) (rs12042763). **Prostate cancer** risk was not related to use of either nonaspirin NSAIDs or **acetaminophen**. These results contribute further evidence that aspirin may have chemopreventive activity against prostate cancer and highlight the need for additional research.

2.36 Ashok, V., C. Dash, et al. (2011). Selective cyclooxygenase-2 (COX-2) inhibitors and breast cancer risk.

Breast. Netherlands, 2010. Published by Elsevier Ltd. 20: 66-70.

BACKGROUND: Recent epidemiologic and laboratory studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of breast cancer through inhibition of cyclooxygenase-2 (COX-2). METHODS: We conducted a case-control study to measure the association between selective cox-2 inhibitors, particularly celecoxib, rofecoxib, valdecoxib and non-specific NSAID subgroups, and breast cancer risk. Between 2003 and 2006, a total of 18,368 incident breast cancer cases were identified in the Ingenix/Lab Rx insurance database, which contains clinical encounter and drug prescription data. Four controls per case were randomly selected, matched on age and time in database. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. RESULTS: Breast cancer risk was inversely associated with both non-specific NSAID and selective COX-2 inhibitor use. Greater than 12 months' duration of use of Celecoxib at a standard dose (200mg/day) was associated with a 16% decrease in breast cancer risk (OR=0.84, 95% CI=0.73, 0.97). We observed the greatest risk reduction in association with >2 years of rofecoxib exposure (OR=0.54, 95% CI=0.37, 0.80). **Acetaminophen**, a compound with less biological plausibility for chemoprevention, showed no significant association with the risk of developing **breast cancer**. CONCLUSION: Consistent with animal models and laboratory investigations, higher doses of selective COX-2 inhibitors were more protective against breast cancer than non-specific NSAIDs. With exposure to rofecoxib, a selective COX-2 inhibitor, breast cancer risk reduction was appreciable (46%), suggesting a possible role for selective COX-2 inhibitors in breast cancer prophylaxis.

2.37 Jacobs, E. J., C. C. Newton, et al. (2011). "A large cohort study of long-term acetaminophen use and prostate cancer incidence."

Cancer Epidemiol Biomarkers Prev 20(7): 1322-8.

BACKGROUND: Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID), particularly long-term use, has been associated with modestly reduced risk of prostate cancer in previous epidemiologic studies. Acetaminophen, a commonly used pain reliever, is not traditionally considered an NSAID but can have anti-inflammatory effects. Few studies have examined the association between long-term acetaminophen use and prostate cancer incidence. METHODS: We examined the association between acetaminophen use and prostate cancer incidence among 78,485 men in the Cancer Prevention Study II Nutrition Cohort. Information on acetaminophen use was obtained from a questionnaire completed at study enrollment in 1992 and updated by using follow-up questionnaires in 1997 and every two years thereafter. Relative risks (RR) were estimated by using proportional hazards regression models. All models were adjusted for age, race, education, body mass index, diabetes, NSAID use, and history of prostate-specific antigen testing. RESULTS: During follow-up from 1992 through 2007, 8,092 incident prostate cancer cases were identified. Current regular use of acetaminophen (30 or more pills per month) for 5 or more years was associated with lower risk of overall prostate cancer (RR = 0.62, 95% CI: 0.44-0.87) and aggressive prostate cancer (RR = 0.49, 95% CI: 0.27-0.88). Current regular use of less than 5 years duration was not associated with prostate cancer risk. CONCLUSION: These results suggest that long-term regular **acetaminophen** use may be associated with lower **prostate cancer** risk. Impact: If the association between acetaminophen use and lower risk of prostate cancer is confirmed, it could provide clues about biological mechanisms that are important in prostate carcinogenesis. Cancer Epidemiol Biomarkers Prev; 20(7); 1-7. (c)2011 AACR.

2.38 Murad, A. S., L. Down, et al. (2011). "Associations of aspirin, nonsteroidal anti-inflammatory drug and paracetamol use with PSA-detected prostate cancer: findings from a large, population-based, case-control study (the ProtecT study)."

Int J Cancer 128(6): 1442-1448.

Evidence from laboratory studies suggests that chronic inflammation plays an important role in prostate cancer aetiology. This has resulted in speculation that nonsteroidal anti-inflammatory drugs may protect against prostate cancer development. We analysed data from a cross-sectional case-control study (n(cases) = 1,016; n(controls) = 5,043), nested within a UK-wide population-based study that used prostate specific antigen (PSA) testing for identification of asymptomatic prostate cancers, to investigate the relationship of aspirin, nonsteroidal anti-inflammatory drug (NSAID) and paracetamol use with prostate cancer. In conditional logistic regression models accounting for stratum matching

on age (5-year age bands) and recruitment centre, use of non-aspirin NSAIDs [odds ratio (OR) = 1.32; 95% confidence interval (CI): 1.04-1.67] or all NSAIDs (OR = 1.25; 95% CI = 1.07-1.47) were positively associated with prostate cancer. There were weaker, not conventionally statistically significant, positive associations of aspirin (OR = 1.13; 95% CI = 0.94-1.36) and **paracetamol** (OR = 1.20; 95% CI = 0.90-1.60) with **prostate cancer**. Mutual adjustment for aspirin, non-aspirin NSAIDs or paracetamol made little difference to these results. There was no evidence of confounding by age, family history of prostate cancer, body mass index or self-reported diabetes. Aspirin, NSAID and paracetamol use were associated with reduced serum PSA concentrations amongst controls. Our findings do not support the hypothesis that NSAIDs reduce the risk of PSA-detected prostate cancer. Our conclusions are unlikely to be influenced by PSA detection bias because the inverse associations of aspirin, NSAID and paracetamol use with serum PSA would have attenuated (not generated) the observed positive associations.

2.39 Ognjanovic, S., C. Blair, et al. (2011). "Analgesic use during pregnancy and risk of infant leukaemia: a Children's Oncology Group study."

Br J Cancer 104(3): 532-536.

BACKGROUND: Infant leukaemia is likely initiated in utero. METHODS: We examined whether analgesic use during pregnancy was associated with risk by completing telephone interviews of the mothers of 441 **infant leukaemia** cases and 323 frequency-matched controls, using unconditional logistic regression. RESULTS: With the exception of a reduced risk for infant acute myeloid leukaemias with non-aspirin non-steroidal anti-inflammatory drugs (NSAID) use early in pregnancy (odds ratios=0.60; confidence intervals: 0.37-0.97), no statistically significant associations were observed for aspirin, non-aspirin NSAIDs, or **acetaminophen** use in early pregnancy or after knowledge of pregnancy. CONCLUSION: Overall, analgesic use during pregnancy was not significantly associated with the risk of infant leukaemia.

2.40 Walter, R. B., F. Milano, et al. (2011). "Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective vitamins and lifestyle (VITAL) study."

J Clin Oncol 29(17): 2424-31.

PURPOSE Among previous studies examining the associations of over-the-counter analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) and incident hematologic malignancies, results were inconsistent for NSAIDs but suggested an increased risk with acetaminophen (paracetamol). Herein, we used a large prospective cohort study to examine these associations. PATIENTS AND METHODS In total, 64,839 men and women age 50 to 76 years were recruited

from 2000 to 2002 to the Vitamins and Lifestyle (VITAL) study. Incident hematologic malignancies (n = 577) were identified through December 2008 by linkage to the Surveillance, Epidemiology and End Results cancer registry. Hazard ratios (HRs) associated with use of analgesics for total incident hematologic malignancies and cancer subcategories were estimated by Cox proportional hazards models. Models were adjusted for age, sex, race/ethnicity, education, smoking, self-rated health, arthritis, chronic musculoskeletal pain, migraines, headaches, fatigue, and family history of leukemia/lymphoma. Results After adjustment, there was an increased risk of incident **hematologic malignancies** associated with high use (>/= 4 days/week for >/= 4 years) of **acetaminophen** (HR, 1.84; 95% CI, 1.35 to 2.50 for high use; P trend = .004). This association was seen for myeloid neoplasms (HR, 2.26; 95% CI, 1.24 to 4.12), non-Hodgkin's lymphomas (HR, 1.81; 95% CI, 1.12 to 2.93), and plasma cell disorders (HR, 2.42; 95% CI, 1.08 to 5.41), but not chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; HR, 0.84; 95% CI, 0.31 to 2.28). By comparison, there was no association with risk of incident hematologic malignancies for increasing use of aspirin, nonaspirin NSAIDs, or ibuprofen. CONCLUSION High use of acetaminophen was associated with an almost two-fold increased risk of incident hematologic malignancies other than CLL/SLL. Neither aspirin nor nonaspirin NSAIDs are likely useful for prevention of hematologic malignancies.

3. OTHER EPIDEMIOLOGICAL PAPERS THAT MAY CONTAIN RELEVANT DATA

These are papers for which the abstracts do not contain results for acetaminophen/paracetamol and cancer risk, but that have a high probablility of containing such results in the body of the paper.

3.1 Holly, E. A., C. Lele, et al. (1999). "Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California"

Am J Epidemiol 150(4): 375-89.

3.2 Nelson, J. E. and R. E. Harris (2000). "Inverse association of prostate cancer and non-steroidal anti-inflammatory drugs (NSAIDs): results of a case-control study."

Oncol Rep 7(1): 169-70.

3.3 Garcia-Rodriguez, L. A. and C. Huerta-Alvarez (2001). "Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs."

Epidemiology 12(1): 88-93.

3.4 Lipworth, L., S. Friis, et al. (2003). "A population-based cohort study of mortality among adults prescribed paracetamol in Denmark."

J Clin Epidemiol 56(8): 796-801.

3.5 Lacey, J. V., Jr., M. E. Sherman, et al. (2004). "Medication use and risk of ovarian carcinoma: a prospective study."

Int J Cancer 108(2): 281-286.

3.6 Marshall, S. F., L. Bernstein, et al. (2005). "Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status."

J Natl Cancer Inst 97(11): 805-812.

3.7 Platz, E. A., S. Rohrmann, et al. (2005). "Nonsteroidal anti-inflammatory drugs and risk of prostate cancer in the Baltimore Longitudinal Study of Aging."

Cancer Epidemiol Biomarkers Prev 14(2): 390-396.

3.8 Rahme, E., J. Ghosn, et al. (2005). "Association between frequent use of nonsteroidal anti-inflammatory drugs and breast cancer."

BMC Cancer 5: 159.

3.9 Sudbo, J., J. J. Lee, et al. (2005). "Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study."

Lancet 366(9494): 1359-1366.

3.10 Anderson, L. A., B. T. Johnston, et al. (2006). "Nonsteroidal anti-inflammatory drugs and the esophageal inflammation-metaplasia-adenocarcinoma sequence."

Cancer Res 66(9): 4975-4982.

3.11 Gill, J. K., G. Maskarinec, et al. (2007). "Nonsteroidal antiinflammatory drugs and breast cancer risk: the multiethnic cohort."

Am J Epidemiol 166(10): 1150-1158.

3.12 Asgari, M. M., S. S. Maruti, et al. (2008). "A large cohort study of nonsteroidal anti-inflammatory drug use and melanoma incidence."

J Natl Cancer Inst 100(13): 967-971.

3.13 Olsen, J. H., S. Friis, et al. (2008). "Use of NSAIDs, smoking and lung cancer risk."

Br J Cancer 98(1): 232-237.

3.14 Dasgupta, K., D. Di Cesar, et al. (2006). "Association between nonsteroidal anti-inflammatory drugs and prostate cancer occurrence."

Cancer J 12(2): 130-135.

3.15 Van Dyke, A. L., M. L. Cote, et al. (2008). "Regular adult aspirin use decreases the risk of non-small cell lung cancer among women."

Cancer Epidemiol Biomarkers Prev 17(1): 148-157.

3.16 Slatore, C. G., D. H. Au, et al. (2009). "Association of nonsteroidal anti-inflammatory drugs with lung cancer: results from a large cohort study."

Cancer Epidemiol Biomarkers Prev 18(4): 1203-1207.