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ABSTRACT & COMMENTARY

Optimizing Bladder Cancer Locoregional Failure Risk: Stratification After Radical Cystectomy Using SWOG 8710

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Dr. Kanani reports no financial relationships relevant to this field of study.

SYNOPSIS: In this study, the authors evaluated and refined previously published risk stratification for locoregional failure (LF) by applying it to a multicenter patient cohort. The original stratification, which was developed using a single-institution series from the Hospital of the University of Pennsylvania (U Penn), produced three subgroups with significantly different LF risk based on pathologic tumor (pT) classification and the number of lymph nodes identified. This model was then applied to patients in Southwest Oncology Group (SWOG) 8710, a randomized trial of RC with or without chemotherapy. LF was defined as any pelvic failure before or within 3 months of distant failure. The authors found that patients in the U Penn cohort and the SWOG cohort had significantly different baseline characteristics. A revised stratification using pT classification, margin status, and the number of lymph nodes identified produced three subgroups with significantly different LF risk in both cohorts: low risk (≤ pT2), intermediate risk (≥ pT3 with negative margins and ≥ 10 lymph nodes identified), and high risk (≥ pT3 with positive margins or < 10 lymph nodes identified) with 5-year LF rates of 8%, 20%, and 41%, respectively, in the SWOG cohort and 8%, 19%, and 41%, respectively, in the U Penn cohort.

SOURCE: Christodouleas JP, Baumann BC, He J, Hwang WT, et al. Optimizing bladder cancer locoregional failure risk stratification after radical cystectomy using SWOG 8710. *Cancer* 2014;120:1272–1280.

The role of postoperative radiation therapy in muscle invasive bladder cancer after radical cystectomy (RC) and bilateral pelvic lymphadenopathy is not well established. Several organizations are considering clinical trials to assess the impact of radiation therapy after RC in high-risk patients. Validated criteria to define a high-risk population are lacking. The authors have previously reported an unvalidated LF risk-stratification model based on a database of 442 patients treated at U Penn between 1990 and 2008 with RC with or without chemotherapy. After surgery, patients were evaluated every 4 months for 2 years, every 6 months until year 5, and then

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annually with routine chest X-rays and bi-annual computed tomography (CT) scans or magnetic resonance imaging (MRI) of the abdomen and pelvis. This model divided patients into three statistically distinct risk groups based on two variables: pathologic tumor classification and total number of benign or malignant lymph nodes identified in the RC pathology specimen. The model indicated that patients with ≤ pT2 tumors were at low risk of LF, those with ≥ pT3 tumors who had ≥ 10 lymph nodes identified were at intermediate risk of LF, and those with ≥ pT3 tumors who had < 10 lymph nodes identified were at high risk of LF.[1]

The purpose of this study was to validate the previously reported risk stratification using patients enrolled in SWOG 8710, which was a randomized trial that compared RC alone versus three cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by RC. This study was conducted between 1987 and 1998 and included 264 patients operated on by 106 different surgeons at 109 different institutions. The recommended evaluation after surgery was every 3 months for the first year, every 6 months for the second year, and yearly thereafter with chest X-rays. Abdominal or pelvic imaging was not required according to the protocol.[2]

The primary endpoint of this study was LF, but overall survival and isolated distant metastasis were also recorded. LF was defined as imaging evidence of recurrence in the pelvic soft tissues or lymph nodes below the aortic bifurcation before or within 3 months after distant metastases (DM). The goal of the external validation was to demonstrate that the original LF stratification produced significantly different subgroups when applied to the SWOG cohort. Fine and Gray regression was used to compare the incidences of LF between subgroups and to determine whether the explanatory power of the original risk stratification could be improved with additional covariates.When comparing the cohort of patients from U Penn to that of SWOG, there were differences between the two groups. The SWOG cohort was younger, with less advanced disease. The SWOG cohort was more likely to have positive or unknown margin status and fewer lymph nodes removed. Patients in the U Penn cohort were more likely to have neoadjuvant chemotherapy, while patients in the SWOG cohort all received adjuvant chemotherapy. In the U Penn cohort and the SWOG cohort, the overall 5-year LF estimates were 18% and 15%, respectively, and the 5-year isolated DM estimates were 17% and 20%, respectively.

Applying the original risk stratification to the SWOG cohort, the 5-year LF estimates were 8%, 29%, and 36% for the low-risk, intermediate-risk, and high-risk groups, respectively. The original risk stratification was not fully validated in the SWOG cohort because the risk of LF was not significantly different between the intermediate-risk and high-risk groups. Regression analysis was used to determine whether LF risk stratification in the SWOG cohort could be improved by the addition of one or more patient characteristics within the model. Of these variables, only margin status was associated significantly with LF when controlling for the original risk stratification. Modifications to the original risk-stratification model were made to include margin status. The revised risk-stratification model is as follows: low risk (≤ pT2), intermediate risk (≥ pT3 with negative margins and ≥ 10 lymph nodes identified), and high risk (≥ pT3 with positive margins or < 10 lymph nodes identified). With the revised risk stratification, the 5-year LF estimates were similar in both cohorts: 8%, 20%, and 40% for the low-risk, intermediate-risk, and high-risk groups, respectively. The 5-year OS estimates were 62%, 39%, and 7% for the low-risk, intermediate-risk, and high-risk groups, respectively, in the SWOG cohort and 60%, 31%, and 10% for the low-risk, intermediate-risk, and high-risk groups, respectively, in the U Penn cohort. The risk-stratification model failed to show a significant difference in terms of 5-year isolated DM estimates among the three risk groups. For low risk, the 5-year isolated DM estimate was about 15% for both cohorts, and the 5-year isolated DM estimates were 20-40% for intermediate and high risk patients.

COMMENTARY

As systemic therapy continues to improve, local control is becoming increasingly

important. There are multiple examples throughout oncology of this concept, and bladder cancer is no exception. Most oncologists have had the experience of caring for patients with pelvic recurrences from a gynecologic cancer, colorectal cancer, prostate cancer, or bladder cancer. Local recurrences can be significantly debilitating for our patients, particularly in the pre-sacral space. In bladder cancer, these recurrences have generally been underreported because of the high rate of distant failure. Local recurrences in the pelvis often precede distant metastasis, as evidenced from a study from MDACC,[3] and locoregional recurrence was an independent variable predicting DM.

Christodouleas et al present a now validated method of identifying patients with a higher risk of recurrence within the pelvis who may benefit from additional local therapy in the form of radiation therapy. The authors should be commended for taking a previously identified model from their institution and applying it to a cohort of prospectively followed patients treated at multiple institutions making the results more applicable to the community oncologist. When the authors ran a model that previously stratified patients into three risk groups and found that it did not "work" on the SWOG cohort, they tweaked the model to include margin status, and this resulted in more robust model that could be considered generalizable. This type of research and statistical modeling is essential in the design and analysis of future clinical trials evaluating the potential benefit of adjuvant therapy. To date, the data regarding the benefit of additional local therapy in the form of radiation therapy are limited. One randomized trial from Egypt reported in 1992 demonstrated a benefit to radiation therapy by decreasing LF rates from 50% to 10%.[4] This study was done prior to the widespread use of neoadjuvant or adjuvant chemotherapy and in a population where squamous cell histology is more prevalent, thus the local failure rates are higher at 50% compared to 40% in the highest-risk patients from the current study combining the U Penn database and the SWOG database. Nevertheless, the study did demonstrate that radiation therapy can reduce local failure rates to 10%. Another study from Milan comparing 130 patients treated with RC alone to a cohort of 32 patients treated with RC and ≥ 50.4 Gy of radiation therapy demonstrated a benefit to the addition of radiation therapy after RC. This retrospective study demonstrated a benefit in disease-free survival and cause specific survival in patients with pN0-Nx patients treated with adjuvant radiation therapy.

The study from Christodouleas et al published in this month's issue of *Cancer* identifies a validated risk-stratification model that oncologist can use to identify patients that may benefit from additional local radiation therapy, forming a basis for additional trials seeking to improve local control. In my opinion, intermediate-risk patients (≥ pT3 with negative margins and ≥ 10 lymph nodes identified) are more likely to benefit from local therapy, as the LF rate is 20% and the 5-year survival is 30-40%. From the above-discussed retrospective studies, I would estimate that post-operative radiation therapy would decrease the recurrence rate to less than 10%. High-risk patients may benefit as well (≥ pT3 with positive margins or < 10 lymph nodes identified); however, the 5-year survival remains poor at ≤ 10% and efforts should be made to decrease the rate of distant metastasis with the use of novel chemotherapy regimens.

References

1. Baumann BC, Guzzo TJ, He J, et al. A novel risk stratification to predict local-regional failures in urothelial carcinoma of the bladder after radical cystectomy. *Int J Radiat Oncol Biol Phys*. 2013;85:81-88.
2. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349:859-866.
3. Pollack A, Zagars GK, Cole CJ, Dinney CP, et al. The relationship of local control to distant metastasis in muscle invasive bladder cancer. *J Urol*. 1995;154:2059-2063.
4. Zaghloul MS, Awwad HK, Akoush HH, Omar S, et al. Postoperative radiotherapy of carcinoma in bilharzial bladder: Improved disease-free survival through improving local control. *Int J Radiat Oncol Biol Phys*. 1992;23(3):511-517.

ABSTRACT & COMMENTARY

Anastrozole: Effective Chemoprevention of Breast Cancer in Postmenopausal Women

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Dr. Shapiro reports no financial relationships relevant to this field of study.

SYNOPSIS: After a median follow-up of 5 years, the aromatase inhibitor, anastrozole decreased the incidence of breast cancer in high-risk postmenopausal women by 53% compared to women receiving a placebo. This was

accomplished with few side effects, mostly small increases in muscle aches and pains, and hot flashes.

SOURCE: Cuzick J, et al. Anastrazole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2014;383:1041-1048.

This international, double-blind, placebo-controlled trial randomized 3,864 post-menopausal women to receive either 1 mg of anastrozole or placebo for 5 years. Entry criteria required a relative risk of breast cancer at least 1.5 times higher than the general population in women aged 60-70 years old, 2 times higher in those aged 45-60 years old and 4 times higher in those participants aged 40-44 years old. The primary endpoint of the study was histologically confirmed breast cancer: invasive cancers or non-invasive ductal carcinoma in situ.

Women in the anastrozole and placebo groups were well balanced for age, parity, age at menarche and menopause, height and weight, body-mass index, previous use of hormone replacement therapy, hysterectomy, first-degree relatives with breast or ovarian cancer, lobular carcinoma in situ or atypical hyperplasia, estrogen receptor positive ductal carcinoma in situ within 6 months, 10-year Tyrer-Cuzick risk, and women using bisphosphonates during the trial.

After a median follow-up of 5 years, 40 women in the anastrozole group (2%) and 85 women in the placebo group (4%) had developed breast cancer (HR 0.47; 95% CI 0.32-0.68, $p < 0.0001$). The predicted cumulative incidence of all breast cancers (including ductal carcinoma in situ) after 7 years was 5.6% in the placebo group and 2.8% in the anastrozole group, suggesting that 36 women would need to be treated with anastrozole to prevent one cancer in 7 years of follow-up.

Anastrozole was associated with significantly reduced risk of all ductal carcinoma in situ (< 1% vs. 1% HR 0.30, $p = 0.009$) and invasive estrogen receptor positive cancers (1% vs. 2% HR 0.42, $p = 0.001$), but there was no difference for invasive estrogen receptor negative cancers (1% vs. 1%, HR 0.79, $p = 0.538$). Interestingly, the frequency of non-breast cancers was significantly lower in the anastrozole group (2% vs. 4%, RR 0.58, $p = 0.005$).

There were 18 deaths in the anastrozole group (two breast cancer, seven other cancers, two cerebrovascular, three cardiac arrest, four other) and 17 in the placebo group (0 breast cancer, 10 other cancers, two cerebrovascular, one cardiac, four other), and no specific causes were more common in one group than the other ($p = 0.836$). Adverse events were reported by 89% of women in both the anastrozole and placebo groups. Although the total number of fractures did not differ between groups, musculoskeletal adverse events (64% vs. 58%, RR 1.10, $p = 0.0001$), including arthralgia (51% vs. 46%, RR 1.10), joint stiffness (7% vs. 5%, RR 1.51), and carpal tunnel syndrome (3% vs. 2%, RR 1.58) were significantly more common in those taking anastrozole. Vasomotor symptoms were common in both groups, but significantly more frequent with anastrozole than placebo (57% vs. 49%, RR 1.15, $p < 0.0001$). Significantly more women taking anastrozole than those taking placebo reported dry eyes (4% vs. 2%, RR 1.45) and hypertension (5% vs. 3%, RR 1.64), but there was no difference in frequencies of thromboembolic events (1%), cerebrovascular events (< 1%) or myocardial infarctions (< 1%). Vaginal or uterine prolapse and vaginal pruritus were significantly reduced with anastrozole.

COMMENTARY

In 2013, the American Society of Clinical Oncology (ASCO) issued new guidelines recommending that chemoprevention (tamoxifen 20 mg per day for 5 years) "should be discussed as an option to reduce the risk of estrogen receptor positive breast cancer" in pre- and postmenopausal women at increased risk for the disease, and that raloxifene (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) "should also be discussed as options for breast cancer risk reduction" in high-risk postmenopausal women.[1] This was the first time that the ASCO recommended the use of an aromatase inhibitor in postmenopausal women, and was based on the results of a single large institution study (MAP.3) that had similar results to the Cuzick anastrozole trial.[2] The National Comprehensive Cancer Network (NCCN) soon followed with its endorsement of exemestane,[3] but the FDA has not yet approved the use of either agent in the chemoprevention setting.

Both the anastrozole and the exemestane studies showed that, compared with placebo, these aromatase inhibitors reduced the risk of breast cancer (both in situ and invasive disease) by at least 50 percent. Although this risk reduction is somewhat higher than that reported for tamoxifen, there are currently no data directly comparing the benefits and risks of either anastrozole or exemestane to tamoxifen, or to each other.

The side-effect profile of the aromatase inhibitors does appear more favorable than that of tamoxifen,

especially the potentially debilitating and life-threatening risks related to thromboembolic events in older individuals taking tamoxifen. Although it is tempting to extrapolate data from what we know is the case in the treatment of breast cancer,[4] neither the exemestane nor the anastrozole prevention studies adequately address the long-term effects of these agents on postmenopausal women who do not have breast cancer. The aromatase inhibitor prevention studies showed no difference in mortality, although there were too few deaths to allow for a meaningful estimate on survival. It is reassuring that the side effects of these agents were relatively few, but questions do remain as to long-term effects of these drugs on bone loss and cardiovascular risk. Furthermore, aromatase inhibitor-induced arthralgia and other musculoskeletal adverse events may limit patient acceptance of these medications.[5]

Chemoprevention of breast cancer is effective yet underutilized. Taken together, these studies do support the use of anastrozole or exemestane as an alternative to tamoxifen for postmenopausal women at high risk for breast cancer who wish to decrease their risk. Although these agents appear to have a relatively favorable toxicity profile, an individual's comorbid conditions, bone density, musculoskeletal complaints, and overall vigor should be part of the risk-benefit analysis regarding their use for the prevention of breast cancer in high-risk postmenopausal women.

References

1. Visvanathan K, et al. Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2013;31:2942-2962.
2. Goss PE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. 2011;364: 2381-2389.
3. NCCN Guidelines for Breast Cancer Risk Reduction, Version 1.2013. http://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf.
4. Cuzick J, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early stage breast cancer: 10-year analysis of ATAC trial. *Lancet Oncol*. 2010;11:1135-1141.
5. Castel LD, et al. Time course of arthralgia among women initiating aromatase inhibitor therapy and a postmenopausal comparison group in a prospective cohort. *Cancer*. 2013;119:2375-82.

ABSTRACT & COMMENTARY

Antihypertensive Treatments and the Prevention of Colorectal Cancer

By William B. Ershler, MD, Editor

SYNOPSIS: In a nested, case-control analysis using a large computerized clinical dataset, a 16% reduction in colorectal cancer incidence was observed after 3 or more years of angiotensin inhibitor and/or angiotensin receptor blocker treatment of hypertension. This modest reduction in risk could be of great significance considering the widespread use of drugs in this class. However, additional confirmatory research is required.

SOURCE: Makar GA, Holmes JH, Yang Yu-Xiao. Angiotensin-converting enzyme inhibitor therapy and colorectal cancer risk. *JNCI*. 2014;106.

There has been considerable interest, even enthusiasm, about the potential role of angiotensin 1-converting enzyme inhibitors (ACEI) in protecting against cancer since the original report 15 years ago demonstrating a 28% reduced cancer incidence among ACEI-treated patients compared with controls.[1] Subsequent studies have failed to demonstrate protection from colorectal cancer (CRC) or cancer in general.[2-4] In a meta-analysis of 70 randomized, controlled trials, no evidence of benefit was observed on cancer incidence or mortality,[5] although this secondary analysis included several small trials of short duration of treatment and was dominated by results from one very large study.[6,7] Thus the question remains open whether drugs in this class protect against incident cancer or malignant proliferation. There have been a number of preclinical studies demonstrating the potential importance of both angiotensin II and renin in promoting both tumor cell proliferation and neovascularization.[8,9]

Currently, ACEIs and/or angiotensin receptor blockers (ARBs) are widely prescribed for the management of hypertension, and whether their use reduces the risk of CRC remains unclear. Taking advantage of a large computerized medical record database, Makar and colleagues sought to determine whether exposure to these agents would have a secondary benefit on CRC incidence. They conducted a nested case-control study using EPIC's General Practice Research Database (1987–2002). The study cohort consisted of hypertensive patients. Case patients were those diagnosed with CRC after the diagnosis of hypertension. Each incident CRC case was compared to 10 control (non-CRC, hypertensive) subjects matched by age, sex, and both calendar year and duration of follow-up. The association between

CRC and ACE-I/ARB exposure was assessed with conditional logistic regression.

There were 2,847 incident CRC cases matched with 28,239 control subjects. The adjusted odds ratios (ORs) of CRC were 0.84 (95% confidence interval [CI] = 0.72 to 0.98; p = .03) for 3 or more years of ACE-I/ ARB therapy and 0.75 (95% CI = 0.58 to 0.97; p = .03) for 5 or more years of exposure. The strength of this association was stronger for those receiving higher doses (OR = 0.53; 95% CI = 0.35 to 0.79; p = .003 for ≥ 3 years of high-dose exposure). Among patients receiving antihypertensive medications, the association with long-term therapy was no longer statistically significant beyond five years, but the benefit of high-dose therapy remained (OR = 0.59; 95% CI = 0.39 to 0.89; p = .01 for ≥ 3 years of high-dose exposure).

COMMENTARY

This study capitalized on a large primary care database in the United Kingdom and found a 16% reduction in CRC incidence after 3 or more years of ACEI/ ARB therapy among patients with a diagnosis of hypertension. The magnitude of this reduction increased with longer exposure and higher dose of therapy. The strengths of this analysis are the large sample size and the careful methodology undertaken. But, as with any retrospective analysis, even those with large datasets and careful design, there are bound to be limitations, and some of which are emphasized in the accompanying editorial.[10] In short, confounding factors, are difficult to control for in a large clinical dataset (e.g., obesity, tobacco use, treatment compliance), and several of these factors might relate both to antihypertensive drug choice and cancer risk. Among hypertensive patients, the selection of ACEI or ARB treatment might be based upon factors such as renal function or BMI that, in themselves, might associate with risk for CRC. Yet, although the risk reduction was modest (16%), there was a dose and duration effect that would support an interaction of ACEI/ARB treatment and cancer protection. If indeed this interaction is confirmed, additional future research will be required to define the mechanism, as this might provide potential targets for future cancer prevention trials. However, although the findings to date are intriguing and potentially very important, it is too early to recommend the use of ACEIs and/or ARBs tor the purpose of CRC prevention.

References

1. Lever AF, Hole DJ, Gillis CR, et al. Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998;352(9123):179-184.
2. Azoulay L, Assimes TL, Yin H, Bartels DB, et al. Long-term use of angiotensin receptor blockers and the risk of cancer. *PLoS One* 2012;7(12):e50893.
3. Boudreau DM, Koehler E, Rulyak SJ, Haneuse S, et al. Cardiovascular medication use and risk for colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17(11): 3076-3080.
4. Friis S, Sorensen HT, Mellemkjaer L, et al. Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based cohort study in Denmark. *Cancer* 2001;92(9):2462-2470.
5. Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *Lancet Oncol*. 2011;12(1):65-82.
6. Barrios V, Escobar C. Angiotensin-receptor blockade, cancer, and concerns. *Lancet Oncol*. 2010;11(9):819-820; author reply 821-822.
7. Meredith PA, McInnes GT. Angiotensin-receptor blockade, cancer, and concerns. *Lancet Oncol*. 2010;11(9):819; author reply 821-822.
8. Chiu T, Santiskulvong C, Rozengurt E. ANG II stimulates PKC-dependent ERK activation, DNA synthesis, and cell division in intestinal epithelial cells. *Am J Physiol Gastrointest Liver Physiol*. 2003;285(1):G1-11.
9. Yasumaru M, Tsuji S, Tsujii M, et al. Inhibition of angiotensin II activity enhanced the antitumor effect of cyclooxygenase-2 inhibitors via insulin-like growth factor I receptor pathway. *Cancer Res*. 2003;63(20):6726-6734.
10. Song M, Giovannucci EL. Antihypertension and colorectal cancer prevention: getting two birds with one stone? *J Natl Cancer Inst*. 2014;106(2):djt438.

An Aspirin a Day, Keeps Ovarian Cancer Away ...

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study.

This article originally appeared in the January 2014 issue of *OB/GYN Clinical Alert*.

SYNOPSIS: In this pooled analysis of more than 7700 ovarian cancer patients and nearly 12,000 controls, low dose aspirin and high dose non-aspirin NSAID use was associated with a risk reduction for invasive epithelial ovarian cancer of 20 to 34% relative to non-users. Acetaminophen use was not associated with a risk reduction, irrespective of dose or frequency.

SOURCE: Trabert B, Ness RB, Lo-Cigani WH, et al., Aspirin, nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: A pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014;106:djt431.

Increasing evidence is emerging linking regular aspirin use and reduced risks of several malignancies. However, the association to invasive ovarian cancer has been inconclusive, largely attributed to low prevalence and small sample sizes. To better understand this relationship, Trabert and colleagues collected individual case data from 12 population-based case–control studies of ovarian cancer. The study sample consisted of 7776 case patients and 11843 control subjects who were accrued between 1992 and 2007. Exposure data were collected regarding use, dose, duration, and frequency. Outcomes were limited to invasive epithelial ovarian, fallopian tube, and primary peritoneal cancer. Patients with low malignant potential and non-epithelial tumors were excluded. In addition, while all histologies were analyzed, a sensitivity analysis of type of serous cancer (high vs. low grade) was conducted due to the underlying biology of these two lesions. Adjustments were made for important confounding factors affecting ovarian cancer risk such as family history, steroidal contraception use, parity, body mass index, race and age, as well as history of endometriosis, tubal ligation, hysterectomy, and estrogen replacement use. Further sensitivity analyses were conducted removing potential factors that were incompletely reported or collected between the various studies. Odds ratios (ORs) for associations of medication use with invasive epithelial ovarian cancer were estimated in individual studies using logistic regression and combined using random effects meta-analysis. Associations between frequency, dose, and duration of analgesic use and risk of ovarian cancer were also assessed. All statistical tests were two-sided. The authors reported that aspirin use was associated with a reduced risk of ovarian cancer (OR = 0.91; 95% confidence interval [CI] = 0.84 to 0.99). Results were similar but not statistically significant for non-aspirin NSAIDs, and there was no association with acetaminophen. In seven studies with frequency data, the reduced risk was strongest among daily (regular) aspirin users (OR = 0.80; 95% CI = 0.67 to 0.96). In three studies with dose information, the reduced risk was strongest among users of low dose (< 100 mg) aspirin (OR = 0.66; 95% CI = 0.53 to 0.83), whereas for non-aspirin NSAIDs, the reduced risk was strongest for high-dose (≥500mg) usage (OR = 0.76; 95% CI = 0.64 to 0.91). The authors concluded that aspirin use was associated with a reduced risk of ovarian cancer, especially among daily users of low-dose aspirin.

COMMENTARY

The relationship between aspirin use and disease has been demonstrated in both retrospective studies and in prospective, randomized clinical trials. The benefits have long been known for cardiovascular risk, and recently the beneficial effects have extended to several solid tumors, including colorectal cancer, esophageal cancer, bladder cancer, endometrial cancer, liver and lung cancer, and female breast cancer.[1] The risk reduction in ovarian cancer is not surprising, as there is a biological/pharmacological link: inflammation.[2] Aspirin and non-aspirin NSAIDs are potent inhibitors of COX, particularly COX-1. Aspirin is an irreversible inhibitor of COX-1, and NSAIDs reversibly inhibit both COX-1 and COX-2 and are distinguished from acetaminophen, which is a more effective inhibitor of COX-2. The observations from the current study would suggest COX-1 is more important to cancer risk reduction. In addition, it is becoming clear that macrophage infiltration is an important survival mechanism for cancer cell support and subsequent angiogenesis.[3] The impact on local microenvironment effects by many pharmacological agents is aggressively being investigated as options for tumor control and, as in the current case, for cancer prevention.

Large population-based studies such as this, in which data are dependent on recall and personal estimation of use over time, is very difficult to interpret. One confounding variable is recall, in which cancer patients are more likely to link exposure to outcome relative to controls. However, other factors are more difficult to tease out such as intermittent regular use or the development of a condition, which might increase the risk for ovarian cancer but is mitigated by increased and episodic use of pharmacological agents to treat the effects of that disorder (e.g. endometriosis). The authors admit they could not clearly evaluate this aspect in the study. However, multiple sensitivity analyses were performed to judge the robustness of the finding and suggest the link is consistent.

It is somewhat curious that low-dose, regular use of aspirin is more efficacious than high-dose aspirin, yet high-dose non-aspirin NSAIDs are more efficacious than low-dose NSAIDs, particularly since the mechanism of action is directed to COX inhibition. In addition, the use of regular high-dose NSAIDs, particularly COX-2 inhibitors, has been associated with increased cardiovascular risks, making it a poor choice for chemoprevention.[4] Nevertheless, low-dose regular aspirin use appears to clear a safety margin that also provides extensive protection against a variety of ailments. This is an extremely important consideration because institution of a chemoprevention strategy risks exposure of large numbers of unaffected individuals who will never attain a benefit from treatment. Ovarian cancer, which has a low annual incidence and overall lifetime risk, is very difficult to study in the general population. Targeting high-risk populations (such as

BRCA mutation carriers or Lynch syndrome patients) may improve the therapeutic index and make prospective trials to document its efficacy a feasible adventure.

References

1. Rothwell PM, Price JF, Fowkes FG, et al: Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012;379:1602-1612.
2. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: Mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst*. 2002;94:252-266.
3. Altinoz MA, Korkmaz R: NF-kappaB, macrophage migration inhibitory factor and cyclooxygenase-inhibitions as likely mechanisms behind the acetaminophen- and NSAID-prevention of the ovarian cancer. *Neoplasma* 2004;51:239-247.
4. Mukherjee D, Nissen SE, Topol EJ: Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.

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2. Scan the QR code to the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

4. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

Continuing Education Questions

1. Which of the following statements is false:

a. The study reported by Christodouleas et al identified three risk groups with different local failure risks after RC.
b. The study reported by Christodouleas et al found that patients completing RC for bladder cancer with ≤ pT2 have < 10% risk of local failure.
c. The study reported by Christodouleas et al identified three risk groups with different DM risks after RC.
d. The study reported by Christodouleas et al identified that if patients have < 10 lymph nodes identified in the pathologic RC specimen, they have a higher risk of LF.

2. Which of the following statements about breast cancer prevention is correct?

a. Anastrozole reduces the risk in high-risk postmenopausal women.
b. Tamoxifen reduces the risk in high-risk postmenopausal women.
c. A and B
d. None of the above

3. In the currently reported case-control analysis, three or more years of hypertension treatment with an angiotensin inhibitor or angiotensin receptor blocker was associated with what level of protection from colorectal cancer?

a. 5%
b. 16%
c. 40%
d. 80%

4. Which of the following best describes the findings in the study of aspirin and cancer risk?

a. Acetaminophen provides a modest risk reduction in ovarian cancer risk.
b. Aspirin dose is associated with a greater beneficial effect as compared to aspirin frequency.
c. NSAID use significantly reduced the risk of ovarian cancer.
d. The analysis set was a collection of summarized patient data from randomized, controlled trials.

[IN FUTURE ISSUES] CML Treatment: At Home or Away?

Clinical Oncology Alert

2014 Reader Survey

To ensure *Clinical Oncology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The results will be used to ensure you are getting the information most important to you.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Either fax the completed questionnaire to 404-492-5933, or return it in the enclosed postage-paid envelope. The deadline is **July 1, 2014**.

In future issues of *Clinical Oncology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. appropriate treatment regimens	O A	O B	O C
2. quality-of-life treatments	O A	O B	O C
3. management of clinical symptoms	O A	O B	O C
4. uninsured patients	O A	O B	O C
5. new drug development	O A	O B	O C
6. breast cancer	O A	O B	O C
7. lung cancer	O A	O B	O C
8. prostate cancer	O A	O B	O C
9. cervical cancer	O A	O B	O C
10. FDA regulations	O A	O B	O C

11. What other topics would you like to see discussed in *Clinical Oncology Alert*? _____

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12. Are the articles in *Clinical Oncology Alert* newsletter written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

13. What type of information not currently provided in *Clinical Oncology Alert* would you like to see added?

Please rate your level of satisfaction with the the items listed:

	A. excellent	B. good	C. fair	D. poor
14. monthly case study	O A	O B	O C	O D
15. Rapid Review	O A	O B	O C	O D
16. the design of *COA*	O A	O B	O C	O D
17. quality of newsletter	O A	O B	O C	O D
18. article selections	O A	O B	O C	O D
19. timeliness	O A	O B	O C	O D
20. quality of commentary	O A	O B	O C	O D
21. clearness of abstracts	O A	O B	O C	O D
22. overall value	O A	O B	O C	O D
23. customer service	O A	O B	O C	O D

24. Please describe your work place:

○ A. private practice ○ B. hospital ○ C. government institution ○ D. research

○ E. Other_____

25. Do you benefit from having important points highlighted in the articles? ○ A. Yes ○ B. No

26. To which other publications or information sources about oncology do you subscribe?

_____

_____

27. Which publication or information source do you find most useful, and why? _____

_____

28. Please list the top three challenges you face in your job today.

_____

_____

_____

29. What do you like most about *Clinical Oncology Alert*?

_____

_____

30. What do you like least about *Clinical Oncology Alert* newsletter?

_____

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31. Has reading *Clinical Oncology Alert* changed your clinical practice? If yes, how? _____

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Contact information_____

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