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Does Ezetimibe Cause Cancer? By Rachel Rich

You may have heard the buzz in the news lately about the lipid-lowering drug ezetimibe and increased risk of cancer. The buzz started over results from a recent clinical trial, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. In this trial, a combination of simvastatin and ezetimibe was compared with placebo to see if there would be a difference in the incidence of cardiovascular events in older people who had aortic-valve stenosis.¹ Unexpected findings revealed a larger incidence of cancer in the treatment group compared to the placebo group. There was an increase in prostate, gastrointestinal, and skin cancer in the treatment group, and an increase in mortality from cancer.

So, does this mean that treatment with simvastatin and ezetimibe causes cancer? Randomized clinical trials are considered the best, most reliable tool for assessment of safety and efficacy of new drugs, but of course they are not perfect. The questions are 1) how strong is the correlation between ezetimibe and cancer, and 2) are these results consistent with other similar trials? The investigators of the SEAS trial acknowledged that further investigation of their unexpected findings was warranted.¹

The hypothesis that adding ezetimibe to statin therapy might increase cancer incidence was a natural progression from the findings of the SEAS trial. This prompted analysts to compare cancer data from two other ongoing trials with similar treatment regimens using the same drugs. These trials were the Study of Heart and Renal Protection (SHARP) trial and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). In these trials, there was no significant overall increased incidence of any specific type of cancer in the treatment group. In the ezetimibe treatment groups, there were more deaths from cancer, but this outcome was not statistically significant⁽²⁾. The combined data from these two trials included information from a total of 20,607 patients, compared to only 1,873 patients in the SEAS trial. The SEAS trial did have a longer mean follow-up time than either the SHARP or IMPROVE-IT trials: 4.1 years compared to 2.7 years and 1 year, respectively. While this may seem significant, only time will tell if continued follow-up of the ongoing trials will yield results to support the cancer hypothesis. Right now, there is no evidence of a trend in the relative risk of death from cancer over time in data from all three trials combined.²

The FDA stated they are investigating the issue of ezetimibe and cancer, but emphasized that patients should not stop taking Vytorin or any other cholesterol-lowering drug. A full safety report on the topic can be expected from the FDA some time in 2009.³ Representative from the Clinical Trials Service Unit at Oxford, UK, indicated “no credible evidence” exists to confirm Vytorin causes cancer. Because the studies in question did not specifically address cancer risk in their hypotheses, further research is needed to clarify any relationship between Vytorin and cancer.⁴

References

1. Drazen JM, D'Agostino RB, Ware JH, Morrissey S, Curfman GD. Ezetimibe and cancer -- an uncertain association. *N Engl J Med.* 2008 Sep 2.
2. Peto R, Emberson J, Landray M, Baigent C, Collins R, Clare R, et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med.* 2008 Sep 2.
3. Early communication about an ongoing safety review of Ezetimibe/Simvastatin (marketed as vytorin), simvastatin (marketed as zocor) and ezetimibe (marketed as zetia). FDA investigates a report from the SEAS trial. [homepage on the Internet]. August 21, 2008. Available from: http://www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin_SEAS.htm.
4. Sir richard peto responds to government questions about vytorin cancer analysis [homepage on the Internet]. . 2008 September 18, 2008. Available from: <http://www.theheart.org/article/906061.do>.

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OTC Products May Interfere with PSA Testing by Shari Hirata

Recent news reports have raised concern that common over-the-counter pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) may interfere with prostate cancer screening tests. A report released on September 8, 2008, by the American Cancer Society Journal, *Cancer*, evaluated the effects of NSAIDs and acetaminophen on prostate specific antigen (PSA) levels in men older than 40 years of age.¹

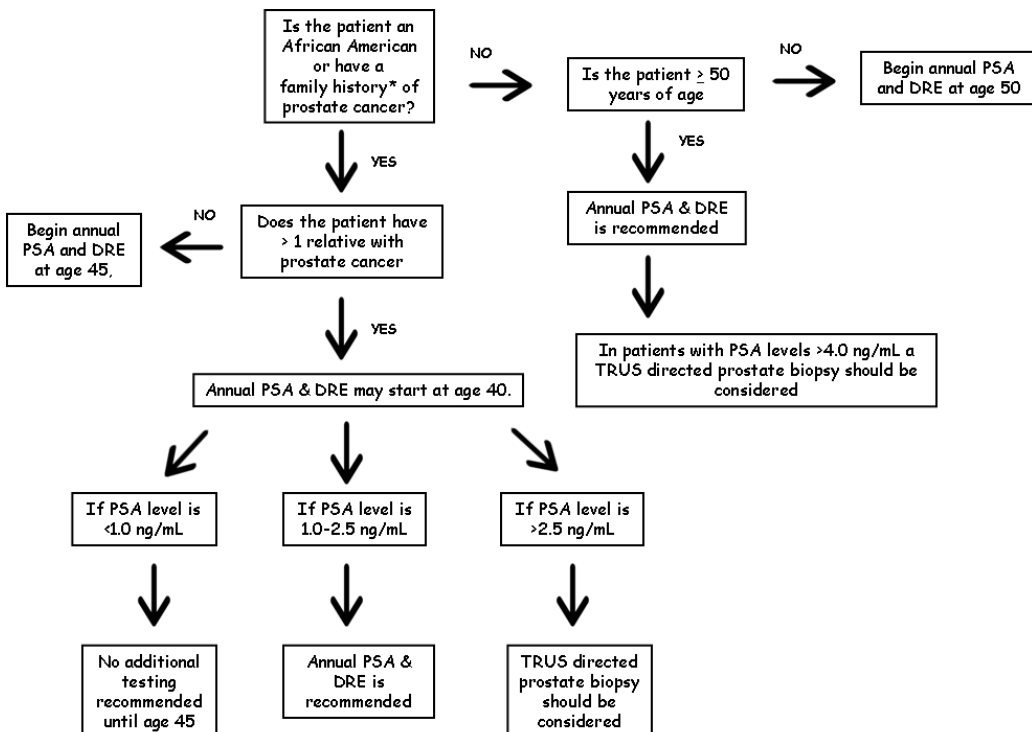
Singer and colleagues conducted a cross-sectional study of 1319 men from the 2001-2002 National Health and Nutrition Examination Survey (NHANES). The primary outcome was the relationship between medication history and PSA levels. The authors concluded that men who used NSAIDs nearly everyday were associated with a 10% lower PSA level than those who did not use NSAIDs (p=0.038).¹ This led to speculation that these medications might decrease detection of prostate cancer.

After review of similar studies which addressed the association between NSAID use and PSA levels, no cause and effect relationship can be determined.^{2,3} Due to the activity of NSAIDs on the cyclooxygenase-2 enzyme (COX-2), NSAIDs are proposed to decrease the remodeling of prostatic epithelium and therefore decrease PSA levels. It is uncertain whether the decrease in PSA found by Singer and colleagues may have been due NSAIDs alone, or if other factors may have been involved. These studies were not designed to determine the magnitude at which PSA levels are decreased and if this decrease is enough to mask possible cancer. At this time, practitioners should not change their practice for prostate cancer screening based on a patient's use of NSAIDs.

The combination of both PSA testing and direct rectal examinations (DRE) are considered first line for assessing the risk of prostate cancer.⁴ Beginning at the age of 50, the American Cancer Society recommends that men be offered annual PSA tests and DRE for individuals who have a life expectancy of at least 10 years. Whether a patient is taking NSAIDs or not, a positive DRE or an elevated PSA is not conclusive and requires further evaluation and a trans-rectal ultrasound (TRUS) directed prostate biopsy should be considered. The American Cancer Society's recommendation for the early detection of prostate cancer is summarized in Table 1. The exact cut-off PSA level of when further evaluation is needed is controversial. A lower cut-off value of 2.5 ng/mL has been shown to improve the detection of organ-confined prostate cancers, but it has also shown to increase the number of biopsies done in men where no cancer is detected.

Table 1 - Prostate Cancer Screenings for Early Detection^{5,6}

* Family history = any first-degree relative (father, brother, or son) who has been diagnosed with prostate cancer at an early age (< 65 years of age).



References

- Singer EA, Palapattu GS, van Wijngaarden E. Prostate-specific antigen levels in relation to consumption of nonsteroidal anti-inflammatory drugs and acetaminophen: Results from the 2001-2002 national health and nutrition examination survey. *Cancer*. 2008;113(8):2053-7.
- Mahmud SM, Tanguay S, Begin LR, Franco EL, and Aprikian AG. Non-steroidal anti-inflammatory drug use and prostate cancer in a high-risk population. *Euro J Cancer* 2006;15:158-164.
- Platz EA, Rohrmann A, Pearson JD, et al. Nonsteroidal Anti-inflammatory Drugs and Risk of Prostate Cancer in the Baltimore Longitudinal Study of Aging. *Cancer Epidemiol Biomarkers Prev* 2005;14:390-396.
- Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Elsevier Inc.; 2007:2677-3931.
- Smith RA, von Eschenbach AC, Wender R, Levin B, Byers T, Rothenberger D, et al. American cancer society guidelines for the early detection of cancer: Update of early detection guidelines for prostate, colorectal, and endometrial cancers. also: Update 2001--testing for early lung cancer detection. *CA Cancer J Clin* 2001;51:39-44.
- American Cancer Society. American Cancer Society web site. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_Can_prostate_cancer_be_found_early_36.asp. Accessed September 17, 2008.

FDA Announces 20 Medications that May Pose Risk by Lauren Fujita

Beginning this year, the Food and Drug Administration (FDA) will post quarterly reports on any serious risks or new safety information that have been reported to the Adverse Event Reporting System (AERS).¹ New safety information includes any unexpected serious risk (death, chance of death, hospitalization, or birth defects/complications), awareness of a new serious risk since the FDA's last assessment, or questions about effectiveness.³ This initiative started with the Food and Drug Administration Amendment Act of 2007 which required bi-weekly reviews of the AERS to be performed along with the report every quarter. These reviews are conducted jointly by the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.¹

Normally, it would take multiple AERS reports in order for a drug to make it on the report; however, in some cases a single AERS report may be enough to lead to further investigation. The report is brief and lists the product name along with its associated risk or new safety information. Once a drug has been reported, it will not appear again on future lists even if additional information becomes available.¹

The FDA has not described the specific process for identifying drugs for inclusion on this list. One concern is that these lists are too simple, lacking important detail such as the severity of the risk or how many cases have been reported for each. Currently, only the drug name and its associated risk is listed.⁴ Although there are questions and concerns revolving around this report, it is believed to be a step in the right direction.

The first report released was for the 1st quarter 2008 (listed below). It is important to remember that these are only preliminary observations, and no causal relationship has been established. Prescribing practices should not be altered based on this report. Questions and concerns should be addressed and discussed between the health care provider and patient. At this time, the identified medications have a possible safety concern, but additional investigation is needed to confirm the information.²

Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) January - March 2008²

Product Name: Active Ingredient (Trade) or Product Class	Potential Signal of Serious Risk/New Safety Information
Arginine Hydrochloride Injection (R-Gene 10)	Pediatric overdose due to labeling / packaging confusion
Desflurane (Suprane)	Cardiac arrest
Duloxetine (Cymbalta)	Urinary retention
Etravirine (Intelence)	Hemarthrosis
Fluorouracil Cream (Carac) and Ketoconazole Cream (Kuric)	Adverse events due to name confusion
Heparin	Anaphylactic-type reactions
Icodextrin (Extraneal)	Hypoglycemia
Insulin U-500 (Humulin R)	Dosing confusion
Ivermectin (Stromectol) and Warfarin	Drug interaction
Lapatinib (Tykerb)	Hepatotoxicity
Lenalidomide (Revlimid)	Stevens Johnson Syndrome
Natalizumab (Tysabri)	Skin melanomas
Nitroglycerin (Nitrostat)	Overdose due to labeling confusion
Octreotide Acetate Depot (Sandostatin LAR)	Ileus
Oxycodone Hydrochloride Controlled-Release (Oxycontin)	Drug misuse, abuse and overdose
Perflutren Lipid Microsphere (Definity)	Cardiopulmonary reactions
Phenytoin Injection (Dilantin)	Purple Glove Syndrome
Quetiapine (Seroquel)	Overdose due to sample pack labeling confusion
Telbivudine (Tyzeka)	Peripheral neuropathy
Tumor Necrosis Factor (TNF) Blockers	Cancers in children and young adults

References:

1. FDA/CDER resources page. Food and Drug Administration Web site. http://www.fda.gov/cder/aers/potential_signals/default.htm. Accessed September 18, 2008.
2. FDA/CDER resources page. Food and Drug Administration Web site. http://www.fda.gov/cder/aers/potential_signals/potential_signals_2008Q1.htm#list. Accessed September 18, 2008.
3. DeNoon D. 20 drugs the FDA is watching. WebMD website. <http://www.webmd.com/news/20080905/20-drugs-fda-is-watching>. September 5, 2008. Accessed September 15, 2008.

Consensus Statement on Treating Pre-Diabetes by Nick Bennett

According to the American Association of Clinical Endocrinologists (AACE), pre-diabetes is defined as having impaired fasting glucose (IFG) (fasting blood glucose levels between 100-125 mg/dL), impaired glucose tolerance (IGT) (2 hour post-glucose load blood level of 140-199 mg/dL), or both states. These patients are at risk for developing type II diabetes at an alarmingly high rate. The goal of treatment in these patients is aimed at decreasing the development of diabetes and the incidence of long-term micro and macrovascular complications.

Patients classified into the pre-diabetes groups (as defined above) should first be encouraged to implement lifestyle modifications with goals of improving glucose control and preventing cardiovascular complications. The following are proposed for lifestyle modifications:

- Weight loss of 5-10% of the patient's baseline weight
- A workout regimen of moderate physical intensity for 30-60 minutes at least 5 days per week
- Implementation of a diet low in fat and sodium as well as increased fibers
- Reducing alcohol intake

There are currently no FDA approved drug therapies for the treatment of pre-diabetes. The goals of drug therapy are to prevent the progression to diabetes and the subsequent microvascular complications. The following are the recommendations regarding drug therapy:

- Literature supports the use of metformin and acarbose as first line therapies in addition to lifestyle changes, and should be given consideration when the following high risk conditions exist: metabolic syndrome, cardiovascular disease, non-alcoholic fatty liver disease, history of gestational diabetes, polycystic ovarian syndrome, worsening blood sugars, or a combination of IFG, IGT, and/or metabolic syndrome.
- Clinical data also favors the use of thiazolidinediones, however, outcome data concerning their safety profile doesn't warrant use as a primary therapy option.

Patients with pre-diabetes should also be screened for lipid, coagulation, and blood pressure abnormalities. Lipid and blood pressure goals are the same as for diabetic patients (LDL <100 mg/dL and <130/80 mm Hg, respectively). The following are the recommendations regarding lipid, blood pressure, and anti-platelet therapy:

- Statin therapy is the primary treatment to lower LDL. Alternative therapy options include fibric acid derivatives, bile acid sequestrants, and ezetimibe. Niacin may be considered but can potentially affect glycemic control.
- First line hypertension agents are Angiotensin Converting Enzyme inhibitors and Angiotensin Receptor Blocking agents, with Calcium Channel Blockers being considered a second-line option. Thiazides and beta-blockers can negatively affect glycemic control and should be used with caution.
- Aspirin is the primary anti-platelet therapy suggested for all patients, unless there is a pre-existing risk for bleeding or other contraindication.

Monitoring recommendations for these patients include an annual oral glucose tolerance test (OGTT), as well as testing for microalbuminuria and biannual FPG, HgbA1C, and lipid panels. Patients whose labs are worsening should have their lifestyle modifications and drug therapy evaluated for potential changes to help return the patient to normal clinical levels.

The consensus statement also includes economic data regarding effective pre-diabetes treatment, as well as recommendations for future studies. Overall, the consensus statement outlines the options for helping patients reduce long term complications and reduce their risk for developing diabetes. The population with pre-diabetes is a great concern as health care practitioners and the use of lifestyle modifications coupled with drug therapy, when appropriate, can help prevent negative outcomes for many patients. Full-text of these recommendations is available at <http://www.aace.com/meetings/consensus/hyperglycemia/hyperglycemia.pdf>.

Reference:

American College of Endocrinology. Consensus statement on the diagnosis and management of pre-diabetes in the continuum of hyperglycemia. July 2008. Accessed at <http://www.aace.com/meetings/consensus/hyperglycemia/hyperglycemia.pdf>.

FDA Releases Stronger Warnings on Arthritis Medications by Peter Fong

With the discovery of the role tumor necrosis factor alpha (TNF α) plays in the pathogenesis of rheumatoid arthritis, advances in drug therapy specifically tailored to target TNF α have provided clinicians another option among disease-modifying antirheumatic drugs (DMARDs). While there are other cytokines that play a role in the complex pathogenesis of rheumatoid arthritis, it is believed that TNF α may be central to this process.¹

Currently, there are four TNF α -inhibitors (TNFIs) available on the market: Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). TNF α -inhibitors are highly effective in treating rheumatoid arthritis; however, their high cost and adverse side effect profile limit their use as first line therapy. DMARDs such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine are considered as first-line therapy, either alone or in combination with another DMARD, if unsuccessful with monotherapy.²

A drug class side effect with the TNFIs is an increased susceptibility to infections. In fact, the United States Food and Drug Administration (FDA) has recently released a safety alert, warning health care professionals that histoplasmosis and other invasive fungal infections are not being consistently recognized in patients being treated with TNF α -inhibitors.³ The alert is the FDA's response to reports of patients developing pulmonary and disseminated histoplasmosis, coccidioidomycosis, and blastomycosis while on TNF α -inhibitors.³ In some cases, these opportunistic infections went unrecognized, causing delayed treatment with antifungal therapy, and resulting in death.³

However, a meta-analysis has shown that TNF α -inhibitors as a class do not cause an increase in the number of infections or severe infections in comparison to placebo or other DMARDs. While TNF α -inhibitors as a class do not increase the risk for infection, data broken down to reflect individual agents has shown that Remicade (infliximab) does indeed cause a statistically significant increase in the risk of infection.⁴ This meta-analysis however, fails to differentiate between the type of infections. This may prove to be critical as Remicade is administered at a greater rate in Europe, where tuberculosis infections are much more prevalent.⁵

Regardless, the number of case reports of opportunistic infections has now prompted the FDA to require manufacturers to strengthen their warnings in relation to invasive fungal infections, such as histoplasmosis.³ This will affect the *Boxed Warning* and *Warnings sections* of the drugs' prescribing information and the Medication Guide for patients.³ Both patients and clinicians should be aware of the risks involved with TNF α -inhibitors.

As TNF α -inhibitors are also considered immunosuppressants, clinicians should closely monitor patients during and after treatment with TNF α -inhibitors for the development of the signs and symptoms of infection. These symptoms include: fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on X-ray, and/or serious systemic illness including shock.³ Should a patient develop any of these symptoms and is suspected to have an infection, a complete diagnostic workup should be performed, which may include fungal cultures, histopathological or cytological evaluations, antigen detection and serum antibody titers.³ Patients with an infection may be restarted on a TNF α -inhibitor only after the infection has resolved.³ However, in the case of a retreatment, the benefits and risks associated with TNF α -inhibitor therapy should be reassessed, especially if the patient resides in an area of endemic mycoses such as the Ohio and Mississippi River valleys of the United States.³

Given the fact that these infections may be life threatening, it is essential for both patients and health care providers to understand the risks and benefits involved with TNF α -inhibitors. Further information may be acquired from the FDA at http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm, or from the Creighton University Center for Drug Information & Evidence-Based Practice.

References:

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet*. 2001; 358 (9285): 903-911.
2. O'Dell JR. Chapter 16. Treatment of rheumatoid arthritis. In: Imboden JB, Hellmann DB, Stone JH, editors. *Current Rheumatology Diagnosis & Treatment*, 2nd Edition. New York: McGraw-Hill; 2007. Accessed from: <http://www.accessmedicine.com/content.aspx?aID=2725074>.
3. Information for Healthcare Professionals Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). US Food and Drug Administration, Center for Drug Evaluation and Research. 2008 Sep [cited 2008 Sep 18] Available from: http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm
4. Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. *BMC Musculoskeletal Disorders*. 2008; 9: 52
5. Hochberg MC, Leibold MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum*. 2005; 34: 819-836.



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