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HIGHLIGHTS AND *EDITORIAL COMMENTS* MAY 2005

Injecting New Enthusiasm into the Dietary Management of Hyperlipidemia

5-1 THE EFFECT OF A PLANT-BASED DIET ON PLASMA LIPIDS IN HYPERCHOLESTEROLEMIC ADULTS

Dietary modifications to lower LDL-cholesterol have focused on avoiding saturated fats and cholesterol. They often result in only modest improvement.

This traditional focus of lipid management may have been overly simplistic. Diets may be more effective if more attention were focused on *including* certain foods rather than just *avoiding* saturated fat and cholesterol. Several foods such as soy protein, plant sterols, soluble fiber, oats, nuts, and garlic have potential lipid benefits. Each is derived from plants. They contain little saturated fat and no cholesterol.

This study theorized that the lipid-lowering benefits of a plant-based diet would be greater than a more conventional low fat-diet under conditions in which both diets contained the same amount of total fat, saturated fat, and cholesterol, and the weight was held steady.

Subjects were randomized to:

1) Low Fat diet. Consistent with former American Heart Association step 1 guidelines:

2) Low-Fat Plus diet. Consistent with the AHA year 2000 guidelines:

Kept saturated fat under 10% but added increased intakes of vegetables and whole grains—in general a plant-based diet. It contained considerably more vegetables, legumes, whole grains, and fruits. Soy protein (~ 16 g per/2000 kcal) and fresh garlic (~ 1.5 cloves) were used daily.

Butter, cheese, and eggs were added to the low-fat plus diet to increase the saturated fat and cholesterol content to match the low-fat diet. Both diets provided 30% of energy from total fat; 10% from saturated fat; and about 100 mg cholesterol per 1000 kcal.

Change at 4 weeks (means):	Low-fat Plus	Low-fat
Total cholesterol (mg/dL)	-18	-9
LDL-cholesterol (mg/dL)	-14	-7

In moderately hypercholesterolemic individuals a plant-based low-fat diet achieved a significantly greater reduction in LDL-c than the standard low saturated fat diet.

The differences are not attributable to saturated fat, cholesterol, energy intake, or body weight because each of these variables was kept constant in the 2 groups.

This puts a new slant on treatment of dyslipidemia. Patients may be told that including 1, 2 or 3 selected foods daily will actually treat their cholesterol.

Combinations of A Statin, A Beta-Blocker, and Aspirin Improve Survival in High-Risk Patients

5-2 EFFECT OF COMBINATIONS OF DRUGS ON ALL-CAUSE MORTALITY IN PATIENTS WITH ISCHEMIC HEART DISEASE

This case-control study assessed the effect of combinations of drugs (statins, aspirin, beta-blockers and angiotensin converting enzyme inhibitors [**ACE**]) in the *secondary* prevention of all-cause mortality in patients with ischemic heart disease.

All-cause mortality:	Adjusted odds ratio (controls/cases)
Statins alone	0.53
Aspirin alone	0.59
ACE alone	0.80
Beta-blocker alone	0.81
Combined statin, aspirin & beta-blocker	0.17
Combined statin, aspirin, beta-blocker, and ACE	0.25

In this secondary prevention study, combinations of statins, aspirin, and beta-blockers improved survival in high-risk patients with IHD.

Millions of Americans are now using multiple drugs for primary, as well as secondary prevention. This includes drugs for hypertension [thiazides, beta-blockers, ACE inhibitors], statins for dyslipidemia, and low-dose aspirin. The absolute benefit will be lower than when used for secondary prevention.

We could include other interventions for both primary and secondary prevention: weight control; physical fitness; modest daily intake of alcohol.

Supplements Containing 800 IU Appear To Reduce Risk Of Fracture; 400 IU Is Inadequate.

5-3 FRACTURE PREVENTION WITH VITAMIN D SUPPLEMENTATION

A Meta-analysis of Randomized, Controlled Trials.

This study estimated the effectiveness of oral vitamin D supplements in preventing hip and non-vertebral fractures in older persons.

A dose of 800 IU was associated with a reduction in relative risk of both hip fracture (RR = 0.74) and non-vertebral fracture (RR = 0.77) compared with calcium supplements alone or placebo. No significant benefit was observed from a dose of 400 IU.

The pooled risks indicate the NNT(to benefit one patient) = 45 for hip fracture and 27 for any non-vertebral fracture.

I believe there will be greater benefit from vitamin D + calcium if they are started at a younger age. Any benefit in older persons who already are osteoporotic and have already sustained a fracture would be minimal.

I believe supplemental calcium is required for most Americans. Our diet is often woefully deficient in calcium.

Benefit/harm-cost ratio is high for both calcium and vitamin D. There is increasing evidence that the dose should be raised to 800 IU in older persons who live indoors.

Vitamin D is a very safe drug.

"Rapid and Judicious Treatment of Diarrhea, Not Antibiotic Prophylaxis, Is the Best Recommendation"

5-4 TRAVELERS' DIARRHEA: HOW TO HIT THE RUNS FOR FIFTY MILLION TRAVELERS

Prophylaxis and Treatment of Travelers' Diarrhea

An article in this issue of Annals reports a new (to the US) antibiotic *treatment* for traveler's diarrhea. **(TD)**. Rifaximin [*Xifaxan*], a non-absorbable antibiotic, was recently licensed for treatment of uncomplicated traveler's diarrhea. The study reports excellent *prophylactic* properties.

The high protection rate of antibiotic prophylaxis has led to the inescapable conclusion that TD is an infectious disease. Putative agents appear to be gram negative enteric bacteria sensitive to many antibiotics. (Doxycycline, trimethoprim-sulfamethoxazole, and fluoroquinolones are effective. However, unlike rifaximin, they are absorbed.) These microorganisms are likely food or water borne. Beware of "dietary mistakes"—fresh unpeeled fruit and ice.

The editorialist has misgivings about a preventive policy that would lead to millions of persons receiving antimicrobial drugs. The most persuasive argument against universal antibiotic prophylaxis is the existence of excellent treatment alternatives that can reduce an episode of TD to a few hours of inconvenience. Antimotility drugs (eg, loperamide—over-the-counter *Imodium-AD* each tablet contains 2 mg) act rapidly and are safe. Bismuth subsalicylate (*Pepto-Bismol*) is also useful for mild disease. For more severe disease, a fluoroquinolone or azithromycin can be added to the loperamide regimen.

"The current recommendation is to supply the at-risk traveler with these drugs to be taken as required for diarrhea, along with the warning to seek medical attention for more severe symptoms." "Rapid and judicious treatment of diarrhea, not antibiotic prophylaxis, is the best recommendation for most travelers."

Travelers to countries where TD is prevalent should take a packet of treatment drugs along.

It Has Been Known For Decades That Pertussis Occurs In Adults. It Is Not A "Zebra" Diagnosis.

5-5 ADULTS ARE WHOOPING, BUT ARE INTERNISTS LISTENING?

Evidence strongly supports the inclusion of pertussis in the differential diagnosis of chronic cough illness (1 month of more) in adults and adolescents. One study reported that patients had visited their physicians as often as 9 times for cough symptoms, and that none of the 153 referrals for cough symptoms persisting for 2 weeks or longer had pertussis documented as a suspected diagnosis. Many respondents were not aware that childhood immunization with pertussis vaccine does not provide lifetime immunity. Many did not know that the nasopharyngeal swab or aspirate is the preferred method for collection of a sample for culture. A minority knew that antimicrobial therapy is indicated for all close contacts of a case-patient.

Clinicians should think of pertussis when a cough illness exceeds 2 weeks.

"Pertussis is a community-acquired disease of persons of all ages and deserves greater attention by physicians for adults."

Confirmation of diagnosis by culture and PCR is difficult and waiting for confirmation will delay treatment. I believe many clinicians will treat chronic-cough illness empirically with antibiotics.

Approximately 1% of Crystalline B12 Given Orally is Absorbed

5-6 ORAL CYANOCOBALAMIN SUPPLEMENTATION IN OLDER PEOPLE WITH VITAMIN B12 DEFICIENCY: *A Dose-finding Trial*

Vitamin B12 deficiency affects mainly older people. Symptoms include anemia, neuropathy, and neuropsychiatric disorders, but deficiency more commonly leads to nonspecific tiredness or malaise.

In the presence of intrinsic factor, and normal functioning of stomach, pancreas and terminal ileum, B12 in food can be absorbed actively with a limited capacity of about 3 ug per meal. The bioavailability of crystalline B12 is unaffected by the underlying causes of deficiency. Approximately 1% is absorbed by passive absorption.

Although deficiency is usually treated by monthly injections of 1000 ug (1 mg), dietary supplements of 1000 to 2000 ug/d administered orally are as effective in correcting biochemical markers of deficiency.

"The lowest dose of oral cyanocobalamin required to normalize mild vitamin B12 deficiency is more than 200 times the recommended daily allowance, which is approximately 3 ug daily."

Harrison's textbook "Principles of Internal Medicine" states that, generally, treatment is given intramuscularly—1000 ug monthly, although daily oral doses of crystalline B12 are also effective. In patients with pernicious anemia, clinicians may prefer to administer B12 intramuscularly as often as weekly until the anemia is controlled. Thereafter, patient preference may guide therapy.

Causes More Cancer Than It Prevents

5-7 ENDOMETRIAL CANCER AND HORMONE REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

Estrogen-only hormone-replacement therapy **(HRT)** increases the risk of endometrial cancer **(EC).** To counteract this effect, many postmenopausal women who have not had a hysterectomy use combined HRT (progestagen + estrogen). The addition of progestagen attenuates or even reverses the estrogen-associated increase in EC.

This large study assessed the relation between different types of HRT and incidence of EC.

Relative risk of EC compared with never-users:

Continuous combined HRT (progestagen daily + estrogen daily—RR = 0.71 (A reduction in risk.)

Combined cyclic HRT (progestagen 10 to 14 days/month—RR = 1.05 (No significant alteration.)

Estrogen alone—RR = 1.45 (Increased risk.)

But the benefit in lowering risk of EC was greatly offset by a rise in breast cancer.

Incidence rates for endometrial cancer and breast cancer per 1000 women over 5 years:

	Continuous combined	Cyclic combined	Estrogen alone	Never users
Endometrial cancer	2.0	3.0	4.9	3.0
Breast cancer	29	28	18	14

Thus, although continuous combined HRT reduced risk of endometrial cancer by 1 in 1000 over 5 years, it was associated with 15 more breast cancers. This is an increase in total cancers of 14 per 1000. Estrogen alone was associated with a lower risk (4 total cancers per 1000 women over 5 years).

Combined estrogen-progestagen causes a greater increase in breast cancer than a reduction in EC. The net effect is an *increase in total cancer risk* with use of HRT, especially combined HRT.

Progestagens, not estrogens, are the main factor increasing risk of BC.

Just think—another extraordinary sea change in clinical application. For decades standard HRT practice insisted that, for women with a uterus, a progestagen be added to estrogen. This on the pain of being accused of malpractice.

"These Results Do Not Support Aggressive Treatment Of Localized, Low-Grade Prostate Cancer."

5-8 20-YEAR OUTCOMES FOLLOWING CONSERVATIVE MANAGEMENT OF CLINICALLY LOCALIZED PROSTATE CANCER. A Natural History Study

This study estimated 20-year survival of men who were diagnosed with clinically localized PC and treated with observation or androgen withdrawal therapy. None received prostatectomy for attempted cure. They were stratified by age at diagnosis and histological findings. It provides an estimate of the natural progression of PC treated conservatively.

Fifty eight % of patients received no treatment; others received androgen suppression (orchiectomy or estrogens). None received radical prostatectomy for attempted cure.

The median observation period was 24 years.

Men with low-grade PC (Gleason score 2 to 4) had a minimal risk of dying from PC during 20 years. Those with high-grade PC (Gleason score 7, 8 to 10) had a high probability of dying from PC within 10 years. Those with scores 5 to 6 had an intermediate risk of dying from PC.

Cumulative mortality from PC up to 20 years after diagnosis stratified by age and Gleason score (*My analysis of Figure p 2099 RTJ*):

Men age 55-59 at diagnosis:	Died from PC
Gleason score 2-4	5%
Gleason score 8-10	90% (10% died of other causes)
Men age 70-74 at diagnosis	
Gleason score 2-4	8%
Gleason score 8-10	58% (42% died of other causes)

The majority of men with high grade PC die from the cancer regardless of their age at diagnosis. The percentage of deaths from PC in older men is *lower* than in younger men because older men have more competing causes of death. Much depends on the man's age at diagnosis.

"Tumor histology still remains the most powerful predictor of disease progression." Men with well-differentiated tumors rarely die of the disease. Men with poorly differentiated tumors frequently die of the disease within 5 to 10 years despite aggressive interventions including androgen deprivation. (The study did not include radical prostatectomy.)

Counseling men with Gleason scores of 5, 6, and 7, and a life expectancy of more than 15 years poses the greatest challenge. Physicians will continue to recommend aggressive treatments in these patients at the time of diagnosis.

The annual rate of progression of PC does not increase after 15 years. "These results do not support aggressive treatment of localized, low-grade prostate cancer."

None of these patients received PSA screening. At present, the natural history of PC is influenced by PSA determinations. I wondered . . . What would have been the natural history if PSA had been available for this study?

A. Many men would have been biopsied. A diagnosis of "cancer' would have caused great continuing anxiety to the patients and family. Some may have changed their lifestyles as a result.

B. Many with low-grade Gleason scores would have undergone radical prostatectomy without benefit, and with risk of serious adverse effects from surgery.

C. Many men with high-grade scores would have undergone radical prostatectomy with no chance of cure.

D. Many older men would have undergone radical prostatectomy without any effect on their life span. They would have died of other causes.

E. Few men would have been cured.

Primary care clinicians should understand the natural history of PC—as much as it can be presently understood—in order to advise men regarding PSA screening, and benefits and adverse effects of surgery. Screening and surgery should tilt toward younger men.

"In Absolute Terms The Reduction In Mortality Is Moderate. Clinical Decision-Making Will Remain Difficult."

5-9 RADICAL PROSTATECTOMY VERSUS WATCHFUL WAITING IN EARLY PROSTATE CANCER

This article reports estimated 10-year results of a trial comparing radical prostatectomy *vs* watchful waiting **(WW)** in patients with early PC.

Cumulative incidence at 10 years:	Surgery (%)	WW (%)	Absolute difference (%)	NNT
Disease-specific mortality	9.6	14.9	5.3	19
Distant metastases	15.2	25.4	10.2	10
Local progression	19.2	44.3	25.1	4
Disease specific survival at 10 y	91%	86%		

(*Note that 45% of the surgery group were not cured [10% died; 15% had metastases; 20% local progression]. 15% of the WW group had no evidence of disease at 10 years.)*

"We found that the reduction in disease-specific mortality as a result of radical prostatectomy was . . . *limited to patients younger than 65 years."* But this observation had limited interpretability because it was based on small numbers of patients.

"In absolute terms the reduction in mortality is moderate. Clinical decision-making will remain difficult."

The slight difference in 10-year disease-specific survival between groups (5%) impressed me. That 45% of the surgery group was not cured is also impressive.

All of these patients received PSA screening. The end-result at 10 years was a very modest (5%) cure rate. The survival rate in the WW group was 85%.

When first introduced, PSA screening was said to be the most important ontological screen yet developed. Now, the bloom seems to be coming off PSA screening. The US Preventive Task Force states that evidence is inconclusive either for or against screening. Dr. Thomas Stamey, who is considered the father of PSA screening,

now states: "Most prostate cancers now removed need not be removed." "It is a cancer that all men will get if they live long enough."

PSA screening is an important consideration in primary care. Before screening, all men should receive adequate information about risks as well as benefits. This applies to older men—especially those with co-morbidity—who request screening. Screening and surgery should tilt toward younger men.

Primary care clinicians who enthusiastically advise PSA screening assume a much greater responsibility for the adverse effects that screening may lead to than when screening is done after persistent requests from the patient.

Still, PSA remains the best screen for PC available today. Many men will continue to request it. Many primary care clinicians will continue to order it without much thought.

Undoubtedly, PSA screening, biopsy, and attempts at curative surgery are grossly over used.

"Is cure necessary when possible?" Not always. "Is cure possible when necessary?" Sometimes

Aggressive And Effective Relief Of The Acute Pain May Reduce The Risk Of Chronic Pain.

5-10 POSTHERPETIC PAIN: WHEN SHINGLES WANES, BUT PAIN DOES NOT

The intensity of the acute pain shortly after onset of shingles is a robust predictor of postherpetic neuralgia **(PHN).** This leads to the tantalizing hypothesis that aggressive and effective relief of the acute pain may prevent, or at least reduce, the risk of chronic pain.

Oral opioid analgesics, in conjunction with antiviral drugs are likely candidates to decrease the incidence of PHN. They are also more effective in treatment of the acute pain. Opioids are relatively well tolerated by elderly patients.

Previous studies have suggested that control of acute pain will reduce the severity and prevalence of chronic pain. I believe this is an important point for primary care. We should go all-out to control the acute pain of HZ, giving adequate doses of opioids without restraint.

We await availability of the live, attenuated HZ vaccine. It does prevent HZ in elderly adults with waning cellular immunity. It lessens incidence and severity of postherpetic neuralgia.

ABSTRACTS MAY 2005

Injecting New Enthusiasm into the Dietary Management of Hyperlipidemia

5-1 THE EFFECT OF A PLANT-BASED DIET ON PLASMA LIPIDS IN HYPERCHOLESTEROLEMIC ADULTS

Dietary modifications to lower LDL-cholesterol have focused on avoiding saturated fats and cholesterol. They often result in only modest improvement.

This traditional focus of lipid management may have been overly simplistic. Diets may be more effective if more attention were focused on *including* certain foods rather than just *avoiding* saturated fat and cholesterol. Several foods such as soy protein, plant sterols, soluble fiber, oats, nuts, and garlic have potential lipid benefits. Each is derived from plants. They contain little saturated fat and no cholesterol.

It is difficult to distinguish between lipid benefits derived from plant-based dietary components and those derived from avoidance of saturated fat and cholesterol.

This study theorized that the lipid-lowering benefits of a plant-based diet would be greater than a more conventional low fat-diet under conditions in which both diets contained the same amount of total fat, saturated fat, and cholesterol, and the weight was held steady.

Conclusion: Plant-based diet augmented the LDL-cholesterol-lowering effect of a low saturated-fat diet.

STUDY

1. Randomized, clinical trial followed 120 adult outpatients (age 30 to 65) for 4 weeks. At baseline, all had elevated LDL-cholesterol levels (130 to 190 mg/dL).
2. Randomized to:
   1) Low Fat diet. Consistent with former American Heart Association step 1 guidelines:
      Saturated fat less than 10% of energy; cholesterol under 300 mg/d. Included many reduced fat prepared food items.
   2) Low-Fat Plus diet. Consistent with the AHA year 2000 guidelines:
      Kept saturated fat under 10% but added increased intakes of vegetables and whole grains. In general a plant-based diet. (See appendix table 1 and table 2 at www.annals.org) It contained considerably more vegetables, legumes, whole grains, and fruits. Soy protein (~ 16 g per/2000 kcal) and fresh garlic (~ 1.5 cloves) were used daily.
3. Butter, cheese, and eggs were added to the low-fat plus diet to increase the saturated fat and cholesterol content to match the low-fat diet. Both diets provided 30% of energy from total fat; 10% from saturated fat; and about 100 mg cholesterol per 1000 kcal. Menus contained foods commonly available from local markets.
4. In both diets, calorie content varied from 1800 kcal to 3000 kcal to keep weight stable.

RESULTS

1. Change at 4 weeks (means):	Low-fat Plus	Low-fat
Total cholesterol (mg/dL)	-18	-9
LDL-cholesterol (mg/dL)	-14	-7

2. The plant-based low-fat diet achieved an additional mean 7 mg/dL lowering of LDL-c compared with the low-fat diet.
3. No significant differences in triglycerides or HDL-cholesterol. However, HDL-c did fall slightly (possible adverse effect).

DISCUSSION

1. In moderately hypercholesterolemic individuals a plant-based low-fat diet achieved a significantly greater reduction in LDL-c than the standard low saturated fat diet.
2. The differences are not attributable to saturated fat, cholesterol, energy intake, or body weight because each of these variables was kept constant in the 2 groups.
3. Whether the lowering of HDL-c that coincides with the lowering of LDL-c would be considered detrimental remains a matter of debate.
4. A plant-based diet benefits BP and coronary heart disease, and is also recommended by the American Cancer Society.

CONCLUSION

Previous diets emphasizing low saturated fat underestimated the potential LDL-cholesterol lowering effects of diet. Nutrient-dense plant-based diet increased the LDL-c lowering effect of a low fat diet.

Annals Int Med May 3, 2005; 142: 725-33 Original investigation, first author Christopher D Gardner, Stanford University Medical School, Los Altos, CA

An editorial in this issue (pp 793-95), first author David JA Jenkins, University of Toronto, Canada comments:

This dietary approach reflects current thinking on how to increase the effectiveness of therapeutic diets. Soy, oats, wheat germ, almonds, peanuts, flaxseed, and garlic independently reduce cholesterol. The greatest reduction in LDL-c in the study was probably due to inclusion of foods with more fiber—specifically viscous fiber—and a higher proportion of vegetable protein. LDL-c decreases rapidly after start of the diet and remains low as long as the diet is followed.

The FDA has permitted claims for heart disease risk reduction for viscous fiber (oat and psyllium), soy protein, plant sterols, and nuts.

Viscous fibers increase bile acid losses; vegetable proteins are associated with reduced hepatic cholesterol synthesis; plant sterols block cholesterol absorption. Nuts are sources of vegetable protein, plant sterols, and monounsaturated fat.

Vegetarians (relatively higher intakes of plant-based foods) have much lower levels of LDL-c. They have reduced incidence of CHD and live longer.

Statins may be added to the diet to further reduce LDL-c. The diet could reduce the amounts of the drug needed to achieve therapeutic goals thus avoiding adverse effect of higher doses.

The study has injected new enthusiasm into the dietary management of hyperlipidemia.

Plant-based diets may have benefits which extend beyond cholesterol reduction.

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Combinations of A Statin, A Beta-Blocker, and Aspirin Improve Survival in High-Risk Patients

5-2 EFFECT OF COMBINATIONS OF DRUGS ON ALL-CAUSE MORTALITY IN PATIENTS WITH ISCHEMIC HEART DISEASE

Combinations of drugs (as proposed by the "polypill" [1]) for patients with ischemic heart disease **(IHD)** have been received with enthusiasm. There has been no direct evidence evaluating these combinations.

This case-control study assessed the effect of combinations of drugs (statins, aspirin, beta-blockers and angiotensin converting enzyme inhibitors [**ACE**]) in the *secondary* prevention of all-cause mortality in patients with ischemic heart disease.

Conclusion: Combinations of a statin, a beta-blocker, and aspirin improve survival in high-risk patients with IHD to a much greater extent than when used alone.

STUDY

1. Prospective, open cohort case-control study analyzed data from 89 practices in the UK to determine the effects of different combinations of drugs on survival of patients with IHD. Median age of patients at index date = 80.
   A. Cases: Patients with IHD who died from all-causes during a follow-up of 8 years. (N = 2266)
   B. Controls: Randomly selected 4 patients with IHD for each case matched for age and sex. All were alive when their matched case died. (N = 9064)
2. In each group, determined exposure to different combinations of statin drugs, aspirin, beta-blockers and ACE inhibitors.
3. Compared all-cause deaths in each group.

RESULTS

1. All-cause mortality:	Adjusted odds ratio (controls/cases)
Statins alone	0.53
Aspirin alone	0.59
ACE alone	0.80
Beta-blocker alone	0.81
Combined statin, aspirin & beta-blocker	0.17
Combined statin, aspirin, beta-blocker, and ACE	0.25

2. The reductions in all-cause mortality were greater in patients with a history of MI. In this group, a combination of aspirin, satins, and beta-blocker was associated with a 90% reduction.

DISCUSSION

1. In this secondary prevention trial, combinations of statins, aspirin, and beta-blockers improved survival in high-risk patients with IHD.
2. Addition of ACE conferred no benefit in mortality despite adjustment for congestive heart failure.

CONCLUSION

In patients with a history of IHD, combined statins, aspirin, and beta-blockers improved survival. The addition of an ACE conferred no additional benefit.

BMJ May 7, 2005; 330: 1059-63 "Primary Care", Original investigation, first author Julia Hippisley-Cox, School of Community Health Sciences, University Park, Nottingham, UK

The combination of multiple drugs in some form is being used by millions of Americans for primary as well as secondary prevention.

1 "A Strategy to Reduce Cardiovascular Disease by 80%" BMJ June 28, 2003; 326: 1419

This article proposed that *all persons* over age 50 take a daily pill containing 6 drugs in low dose—3 antihypertension drugs [a thiazide, a beta-blocker, and an ACE inhibitor], a statin, aspirin, and folic acid [to reduce homocysteine levels]. The proposal was based on the almost universal prevalence of cardiovascular risk factors in our society. The article received great interest, although it is too extreme for acceptance for general use for primary prevention.

An editorial in this issue of BMJ (pp 1035-36) first author Tom Fahey, University of Dundee, UK comments:

The underlying tenet of the polypill—that combination therapy is better than monotherapy—may well be correct in regard to secondary prevention. Use for primary prevention is more problematic. Recent evidence concerning the differential effect of aspirin in women is emerging. ["A randomized Trial of Low-dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women" NEJM 22005; 352: 1293-304] While the benefit of aspirin is established in men, low-dose aspirin did not result in a reduction in all-cause mortality or myocardial infarctions in women. Benefits of folic acid may be overstated.

The primary prevention approach exposes people at lower risk to lifelong treatment with attendant medicalization of the population and costs. Preventive treatment in persons at high risk may be more reasonable.

Consider patient preference.

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Supplements Containing 800 IU Appear To Reduce Risk Of Fracture; 400 IU Is Inadequate.

5-3 FRACTURE PREVENTION WITH VITAMIN D SUPPLEMENTATION

A Meta-analysis of Randomized, Controlled Trials.

This study estimated the effectiveness of oral vitamin D supplements in preventing hip and non-vertebral fractures in older persons.

Conclusion: Supplements containing 800 IU appear to reduce risk of fracture; 400 IU is inadequate.

STUDY

1. Meta-analysis included 5 trials for risk of a first hip fracture (n = 9200) and 7 trials for risk of first non-vertebral fracture (n = 9800). Only double-blind, randomized, controlled trials were included. Only effects in the white race were determined.
2. All trials used oral cholecalciferol *(vitamin D3) vs* calcium supplements alone or placebo. Dose of vitamin D = 400 IU and 800 IU.

3. All subjects were age 60 and over at time of administration. (Many were in the 80s.)
4. Duration of therapy = 24 to 60 months.

RESULTS

1. A dose of 800 IU was associated with a reduction in relative risk of both hip fracture (RR = 0.74) and non-vertebral fracture (RR = 0.77) compared with calcium supplements alone or placebo. The study did not assess the role of calcium supplementation in addition to vitamin D.
2. No significant benefit was observed from a dose of 400 IU.
3. A higher level of achieved 25-hydroxyvitamin D was associated with greater reductions in fracture.

DISCUSSION

1. The reduction in risk of a hip fracture and any non-vertebral fracture associated with the 800 IU dose (with and without calcium supplementation) was statistically significant.
2. The pooled risks indicate the NNT(to benefit one patient) = 45 for hip fracture and 27 for any non-vertebral fracture.
3. 400 IU was *not* effective.
4. What might be the reason for the benefit? 1) an increase in bone density; 2) an increase in balance and muscle strength; 3) a decreased risk of falling. All have been described as a result of vitamin D supplementation.
5. The 800 IU dose is higher than the current recommended vitamin D intake (400 IU) for middle-aged and older adults "In the current uncertainty about vitamin D intake recommendations, our results support increasing the suggested dose."
6. It is possible that still higher doses will be needed for patients with low baseline 25-hydroxyvitamin D levels.
7. No evidence was found that the effect of vitamin D supplementation increased with duration of trials. (The benefit of the vitamin on increasing strength and reducing risk of falls occurs early.) "However, benefits from starting supplementation earlier in life and continuing beyond 5 years cannot be excluded."

CONCLUSION

Oral vitamin D in a dose of 800 IU appears to reduce risk of hip and non-vertebral factures in elderly persons.

JAMA May 11, 2005; 293: 2257-64 Original investigation, first author Heike A Bischoff-Ferrari, Harvard School of Public Health, Boston, Mass.

A study by The Randomized Evaluation of Calcium OR vitamin D, RECORD Trial Group in Lancet May 7, 2005; 365: 1621-28 "Oral vitamin D3 and calcium for *secondary* prevention of low-trauma fractures in elderly people" reported that supplements of vitamin D3 + calcium did not prevent subsequent fractures. All subjects were over age 70 at baseline (mean age 77).

An editorial in Lancet May 7 , 2005; 365: 1599-1600 by Philip Sambrook, Royal North Shore Hospital Sydney, Australia, "Vitamin D and fractures: Quo vadis?" comments on the RECORD trial. He asks: Have we come to an erroneous conclusion about vitamin D and its relation to fractures? He concludes that, overall, the data are consistent with a therapeutic benefit of vitamin D on fractures in people deficient in vitamin D. The effect on vitamin-D-replete individuals is less clear. Compliance by older people is a problem.

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"Rapid and Judicious Treatment of Diarrhea, Not Antibiotic Prophylaxis, Is the Best Recommendation"

5-4 TRAVELERS' DIARRHEA; HOW TO HIT THE RUNS FOR FIFTY MILLION TRAVELERS AT RISK:

Prophylaxis and Treatment of Travelers' Diarrhea

An article in this issue of Annals reports a new (to the US) antibiotic *treatment* for traveler's diarrhea. **(TD)**[1]. Rifaximin [*Xifaxan*], a non-absorbable antibiotic, was recently licensed for treatment of uncomplicated traveler's diarrhea. The study reports excellent *prophylactic* properties.

Enterotoxigenic *E coli* is the major pathogen of TD. But it accounts for fewer than half of the cases. Advanced microbiological methods have failed to identify a known pathogen in many of the remaining cases.

The high protection rate of antibiotic prophylaxis has led to the inescapable conclusion that TD is an infectious disease. Putative agents appear to be gram negative enteric bacteria sensitive to many antibiotics. (Doxycycline, trimethoprim-sulfamethoxazole, and fluoroquinolones are effective. However, unlike rifaximin, they are absorbed.) These microorganisms are likely food or water borne. Beware of "dietary mistakes"—fresh unpeeled fruit and ice.

The editorialist has misgivings about a preventive policy that would lead to millions of persons receiving antimicrobial drugs, especially a newly introduced drug. Often TD is a minor, self-limited illness. Fewer than 1%of travelers are hospitalized. Increasing the burden of antimicrobial use and the risk of resistance is an ecologically unsound practice. Some drugs used to treat TD have already lost their effectiveness. Rising resistance rates endanger the current standard treatment, a fluoroquinolone.

The most persuasive argument against universal antibiotic prophylaxis is the existence of excellent treatment alternatives that can reduce an episode of TD to a few hours of inconvenience. Antimotility drugs (eg, loperamide over-the-counter *Imodium-AD* each tablet contains 2 mg) act rapidly and are safe. Bismuth subsalicylate (*Pepto-Bismol*) is also useful for mild disease. For more severe disease, a fluoroquinolone or azithromycin can be added to the loperamide regimen.

"The current recommendation is to supply the at-risk traveler with these drugs to be taken as required for diarrhea, along with the warning to seek medical attention for more severe symptoms." "Rapid and judicious treatment of diarrhea, not antibiotic prophylaxis, is the best recommendation for most travelers."

The cited study shows that rifaximin is effective for preventing TD. This does not strengthen the case for universal prophylaxis. Rather it adds an excellent alternative that will be valuable for selected patients.

Annals Int Med May 17, 2005; 142: 861-62 Editorial by Sherwood L Gorbach, Tufts University School of Medicine, Boston, Mass.

1 "A Randomized, Double-blind, Placebo-controlled Trial of Rifaximin to Prevent Travelers' Diarrhea" Annals Int Med May 17, 2005; 142: 805-12 Original investigation, first author Herbert L DuPont, University of Texas-Houston.

The Johns Hopkins Antibiotic Guide (hopkins-abxguide.org) adds some details about TD:

The illness is often benign and self-limited; duration 1 to 5 days.

Treatment is based on symptoms:

a. Mild illness 1-2 stools /24 hours:

Loperamide 4 mg loading dose followed by 2 mg after each loose stool.

Max /24h = 16 mg, or,

Bismuth subsalicylate two 262 mg tablets chewed 4 times daily, or 30 mL every hour,

Max = 8 doses / 24 hours.

Kaopectate 30 mL after each loose stool for up to 7 doses per day will result in more formed stools. It is not absorbed.

B. Moderate illness over 2 stools per 24 hours; watery diarrhea:

Fluoroquinolone, a single dose of once-daily capsule + loperamide. If dysentery persists, complete 3 days. Avoid bismuth subsalicylate, it will chelate fluoroquinolone.

Rifaximin, a non-absorbed antibiotic used for non-invasive *E coli*. It is NOT recommended for systemic infections—diarrhea complicated by fever or bloody stool, or persistent symptoms (> 24-48 h).

Under special circumstances related to important commitments, some travelers may choose to use prophylactic therapy. Rifaximin may be a good alternative.

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It Has Been Known For Decades That Pertussis Occurs In Adults. It Is Not A "Zebra" Diagnosis.

5-5 ADULTS ARE WHOOPING, BUT ARE INTERNISTS LISTENING?

From 1990 to 2001, the incidence of pertussis in adults has increased by 400%. Although pertussis may be responsible for up to one fourth of cases of cough lasting more than 2 weeks in adults and adolescents, physicians have generally considered pertussis a pediatric disease.

A lack of knowledge and myths about pertussis prevent this illness from being recognized as an important cause of community-acquired respiratory disease that may be fatal in infants. It has been estimated that more than 1 million cases occur in the US each year.

It has been known for decades that pertussis occurs in adults. It is not a "zebra" diagnosis.

Evidence strongly supports the inclusion of pertussis in the differential diagnosis of chronic cough illness (1 month of more) in adults and adolescents. One study reported that patients had visited their physicians as often as 9 times for cough symptoms, and that none of the 153 referrals for cough symptoms persisting for 2 weeks or longer had pertussis documented as a suspected diagnosis. Many respondents were not aware that childhood

immunization with pertussis vaccine does not provide lifetime immunity. Many did not know that the nasopharyngeal swab or aspirate is the preferred method for collection of a sample for culture. A minority knew that antimicrobial therapy is indicated for all close contacts of a case-patient.

Unfortunately, diagnosis and treatment are not as straightforward for pertussis as for many other infectious diseases. Serological tests are not usually standardized and are not considered reliable. The direct fluorescent antibody test has problems with false positives. The preferred test is the nasopharyngeal aspirate or swab for polymerase chain reaction and culture confirmation. But, a negative test does not rule out pertussis. "Testing is not sufficiently sensitive for treatment decisions to be guided by test results alone."

One reason cited for lack of recognition of pertussis is that the disease is often mild. Some adults will not even have a cough. The disease can present along a spectrum of disease, including weeks of cough.

Clinicians should think of pertussis when a cough illness exceeds 2 weeks. Empirical treatment of a suspected case may interrupt further transmission, but. . ."Is not itself good medical or public health practice".**1**

Treatment: Erythromycin 14 days is the first-line choice for both treatment and prophylaxis. Better-tolerated clarithromycin and azithromycin are alternatives. A 5-day course of azithromycin has close to the same effect as 14 days of erythromycin.

"To adequately interfere with transmission of this disease, it is important that close contacts are identified and treated regardless of lack of symptoms, age, and even immunization history." Clinicians generally do not have the time to interview and ensure that prophylaxis is received by close contacts. They should call on their local Health Department for help.

An adolescent and adult booster vaccine will probably soon become available and may be incorporated into adult immunization schedules—eg, added to tetanus and diphtheria every 10 years.

"Pertussis is a community-acquired disease of persons of all ages and deserves greater attention by physicians for adults."

Annals Int Med May 17, 2005; 142: 832-35 "Perspective", editorial by Mark S Dworkin, Illinois Department of Health, Chicago.

1 I believe many primary care clinicians will disagree, and will treat patients empirically. Confirmation of diagnosis beforehand seems complicated and will delay treatment. Use of antibiotics for these few cases will not likely lead to adverse effects.

The Johns Hopkins Antibiotic Guide (hopkins-abxguide.org) offers some additional comments about pertussis:

> Pertussis is often unrecognized in adolescents and adults. Prior immunization can lead to atypical presentation.
>
> About 1/5 of patients may develop radiographic infiltration.
>
> It is most often misdiagnosed as bronchitis, 20-30% of adolescents and adults with cough for greater than one week may have pertussis. Average duration of cough is 50 days before the diagnosis is suspected.
>
> Highest incidence is reported in adult healthcare workers.
>
> Most strains are sensitive to both macrolides (erythromycin and others) and fluoroquinolones. They are

resistant to beta-lactams (penicillin).

Macrolides are the first line of therapy. Most experience has been with erythromycin. Clarithromycin (Biaxin) has been equally effective and better tolerated.

Recommended treatment: Clarithromycin 500 mg twice daily, or erythromycin base 250 mg four times daily or erythromycin ethylsucccinate 400 mg four times daily. The recommended treatment duration is 7-14 days.

Azithromycin and fluoroquinolones have excellent in vitro sensitivity profiles, but clinical experience for treating *B pertussis* is limited

Gold standard for diagnosis is culture of nasopharyngeal secretions. Plate on Bordet-Gengou medium for 7 days. However, sensitivity is low. PCR-based assays have been developed.

Increasing incidence in adults may be due to waning immunity. Adult booster vaccinations are currently NOT recommended.

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Approximately 1% of Crystalline B12 Given Orally is Absorbed

5-6 ORAL CYANOCOBALAMIN SUPPLEMENTATION IN OLDER PEOPLE WITH VITAMIN B12 DEFICIENCY: *A Dose-finding Trial*

Vitamin B12 deficiency affects mainly older people. Symptoms include anemia, neuropathy, and neuropsychiatric disorders, but deficiency more commonly leads to nonspecific tiredness or malaise.

In the cell, B12 acts as a cofactor for the enzyme which remethylates homocysteine **(Hcy)** to methionine. Deficiency of B12 leads to increased homocysteine levels. In addition, a deficiency of B12 leads to elevated plasma levels of methylmalonic acid **(MMA).** Elevated plasma levels of Hcy and MMA are markers of deficiency. B12 therapy decreases both.

In the presence of intrinsic factor, and normal functioning of stomach, pancreas and terminal ileum, B12 in food can be absorbed actively with a limited capacity of about 3 ug per meal. The bioavailability of crystalline B12 is unaffected by the underlying causes of deficiency. Approximately 1% is absorbed by passive absorption.

Although deficiency is usually treated by monthly injections of 1000 ug (1 mg), dietary supplements of 1000 to 2000 ug/d administered orally are as effective in correcting biochemical markers of deficiency.

This randomized, double-blind determined the lowest dose of oral B12 required to normalize biochemical markers of deficiency in older persons (mean age 80) with mild deficiency. All had elevation of plasma MMA and Hcy levels, and low B12 levels. Effectiveness of the oral B12 therapy was measured by a decrease in Hcy and MMA levels and an increase in B12 levels.

After testing oral doses from 2.5 ug to 1000 ug, for 16 weeks, the investigators report that the lowest dose required varied from 650 to 1000 ug/d.

“The lowest dose of oral cyanocobalamin required to normalize mild vitamin B12 deficiency is more than 200 times the recommended daily allowance, which is approximately 3 ug daily.”

Archives Int Med May 23, 2005; 165: 1167-72 Original investigation, first author Simone J P Eussen, Wageningen University, the Netherlands.

Causes More Cancer Than It Prevents

5-7 ENDOMETRIAL CANCER AND HORMONE REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

Estrogen-only hormone-replacement therapy **(HRT)** increases the risk of endometrial cancer **(EC).** To counteract this effect, many postmenopausal women who have not had a hysterectomy use combined HRT (progestagen + estrogen). The addition of progestagen attenuates or even reverses the estrogen-associated increase in EC.

This large study assessed the relation between different types of HRT and incidence of EC.

Conclusion: Combined HRT reduces risk of estrogen-related EC. But increases risk of breast cancer.

STUDY

1. Followed over 214 000 women who reported they had used combined HRT and over 14 000 who used estrogen alone. None had a hysterectomy.
2. Compared risk of EC over 3.4 years.

RESULTS

1. Relative risk of EC compared with never-use:
   1) Continuous combined HRT (progestagen daily + estrogen daily—RR = 0.71 (A reduction in risk.)
   2) Combined cyclic HRT (progestagen 10 to 14 days/month—RR = 1.05 (No significant alteration.)
   3) Estrogen alone—RR = 1.45 (Increased risk.)
2. Incidence rates for endometrial and breast cancer per 1000 women over 5 years:

	Continuous combined	Cyclic combined	Estrogen alone	Never users
Endometrial	2.0	3.0	4.9	3.0
Breast cancer	29	28	18	14

(Thus, although continuous combined HRT reduced risk of endometrial cancer by 1 in 1000 over 5 years, it was associated with 15 more breast cancers. This is an increase in total cancers of 14 per 1000. Estrogen alone was associated with a lower risk (4 total cancers per 1000 women over 5 years).

DISCUSSION

1. Breast cancer is much more common than endometrial cancer. When the two cancers were considered together, the total incidence of cancer is dominated by breast cancer.
2. Compared with never-users of HRT, the overall incidence of endometrial cancer was increased in users of estrogen alone, and decreased in users of continuous combined HRT.
3. The effect of commonly used types of HRT varied depending on a woman's body-mass index. Obese women normally have substantially higher incidence of EC than non-obese women. (They produce more estrogen in their fat tissue.) Use of combined HRT reduced incidence of EC in obese women to a greater extent than in thin women.
4. In the UK (as in the US) authorities have long advised against use of estrogen-alone HRT therapy in women

with a uterus for fear of causing EC. Use of estrogen-alone therapy was relatively less common in this study.

CONCLUSION

Progestagens counteract the adverse effect of estrogen on the endometrium, the effect being greater the more days per month they are added to estrogen.

However, combined estrogen-progestagen causes a greater increase in breast cancer than a reduction in EC. The net effect is an *increase in total cancer risk* with use of HRT, especially combined HRT.

Lancet April 30, 2005; 365: 1543-51 Original investigation by the Million Women Study Group, Radcliffe Infirmary, Oxford, UK

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The following 2 articles continue the struggle to untangle the question. . . What is proper screening and treatment for prostate cancer? Screening is an important consideration for primary care. It requires careful thought.

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"For now, the true natural history of today's cases of prostate cancer remains a mystery"

5-8 20-YEAR OUTCOMES FOLLOWING CONSERVATIVE MANAGEMENT OF CLINICALY LOCALIZED PROSTATE CANCER.

"To determine the need for treatment of localized prostate cancer (PC), patients and physicians must understand the natural history of this disease."

The appropriate therapy for men with clinically localized PC is uncertain. A recent report from Scandinavian suggested that the mortality rate from PC increased for men after they had survived 15 years following diagnosis. (A late spurt in death rate.)

This study estimated 20-year survival of men who were diagnosed with clinically localized PC and treated with observation of androgen withdrawal therapy. Outcomes were stratified by age at diagnosis and histological findings. It provides an estimate of the natural progression of PC treated conservatively.

Do PC mortality rates decline, remain constant, or increase after15 years?

Conclusion: The annual mortality rate appears to remain constant after 15 years. This. . . "Does not support aggressive treatment for localized low-grade prostate cancer".

STUDY

1. This retrospective population-based cohort study concerned 767men age 55 to 74 (mean age = 69) with clinically localized PC diagnosed between 1971 and 1984. None underwent surgery, radiation, or brachytherapy.
2. About 71% were diagnosed following transurethral resection or open prostatectomy for benign prostatic hyperplasia; 26% by needle biopsy.
3. Cancers were graded according to the Gleason system which stratifies PC into 1 of 5 morphological patterns

according to the glandular differentiation and growth pattern. (1 indicates well-differentiated doses and 5 poorly differentiated.) The Gleason score represents the sum of pattern numbers of the 2 most common patterns by volume. Scores range form 2 to 10 (10 being the most severe.)

4. 58% of patients received no treatment; others received androgen suppression (orchiectomy or estrogens). None received radical prostatectomy for attempted cure.
5. No information was available concerning the prostate specific antigen (PSA). The study began before PSA became available.
6. The median observation period was 24 years.

RESULTS

1. Prostate cancer mortality rate (per 1000 person-years): first 15 years = 33; after 15 years = 18. (This study did not agree with the Scandinavian study.)
2. Men with low-grade PC (Gleason scores 2 to 4) had a minimal risk of dying form PC during 20 years. Those with high-grade PC (Gleason scores 7 and 8 to 10) had a high probability of dying from PC within 10 years. Those with scores 5 & 6 had an intermediate risk of dying from PC.
3. Most men with high-grade PC died from the cancer regardless of age at diagnosis.
4. Survival and cumulative mortality for PC and other causes up to 20 years after diagnosis stratified by age and Gleason score. (*my analysis of figure p 2099*):

Men are 55-59 at diagnosis:	Died for PC
Gleason score 2-4	5%
Gleason score 8-10	90% (10% died of other causes)
Men age 70-74 at diagnosis	
Gleason score 2-4	8%
Gleason score 8-10	58% (42% died of other causes)

5. Correlation with age over a 20-year period:
   A. For Gleason scores up to 6, death due to PC rose progressively as patients age. Death from PC was greater in older men than in younger men.
   B. For those with Gleason scores 8-10, there were essentially no survivors, regardless of age at diagnosis. However, the percentage of deaths in older men was *lower* than in older men because older men have more competing causes of death. (Older men are more likely to die with the disease than from the disease.)

DISCUSSION

1. “Trends in population-based incidence and mortality rates suggest that a significant number of prostate cancers identified by PSA testing are unlikely to be clinically symptomatic.”
2. Controversy surrounds the appropriate treatment for newly-diagnosed PC. Widespread testing by PSA

introduces lead-time bias[2] and length-time bias[3], effects that further complicate the determination of the true natural history of PC.

3. The previously cited study from Scandinavia which reported an increase in PC mortality rates 15 years and longer after diagnosis is not supported by this 2-year study.
4. "Tumor histology still remains the most powerful predictor of disease progression." Men with well-differentiated tumors rarely die of the disease. Men with poorly differentiated tumors frequently die of the disease within 5 to 10 years despite aggressive interventions including androgen deprivation. (The study did not include radical prostatectomy.)
5. Men with moderately differentiated tumor have the greatest variation in outcomes.
6. Due to co-morbidity, the cause of death in elderly men who have multiple chronic diseases can be difficult to determine.
7. Much depends on the man's age at diagnosis.

CONCLUSION

Patients with low-grade PC have only a small risk of progression even after 20 years. Most patients with high-grade PC die of the disease within 10 years regardless of their age at diagnosis.

The annual rate of progression of PC does not increase after 15 years. "These results do not support aggressive treatment of localized, low-grade prostate cancer."

JAMA May 4, 2005; 293: 2095-2102 Original investigation , first author Peter C Albertsen, University of Connecticut Health Center, Framingham.

1 Natural history of early, localized prostate cancer" JAMA 2004; 291: 2713-19 [See *Practical Pointers* June 2004 [6-3]

2 Lead time: The time between diagnosis (eg, by PSA and biopsy) and a defined event (eg, clinical diagnosis by signs and symptoms, or death from the disease).

PSA screening exacerbates the difficulty in determining the natural history of PC by increasing lead time for many years. At age 55, a diagnosis of PC by PSA extends the lead time to 12 years, and the likelihood of detecting clinically insignificant disease is in the range of 27%. At age 75, the lead time is 6 years, and the likelihood of detecting clinically insignificant disease is increased to 56%.

3 Length time: Refers to the effects of frequency of screening tests (length between).

Contrast: 1) A PSA done yearly with 2) a PSA done every 5 years. Assume the patient did not have an elevated PSA or PC at year); the onset of his PC was 6 months later. At year 1, the PC would be diagnosed by PSA screening. The PC would be at an early stage of development. If the PC were detected for the first time by that PSA screen done at 5 years, the cancer would have had 4 1/2 years to grow.

Frequent PSA screening has a downside. It detects clinically insignificant PCs. One study reported that annual PSA testing from ages 55 to 67 would detect insignificant PC in about half of the men, and would increase a person's lifetime risk of being diagnosed with PC by 80%

"The pool of subclinical PC is much larger than PC mortality statistics would suggest."

The study does not define the true natural history of PC. We have no way of determining when the disease starts. It may be a short time or a long time before diagnosis. PSA screening has changed our concept of the natural history, but we still do not fully understand it.

An editorialist, Peter H Gunn, Northwestern University, comments in an editorial (JAMA May 4, 2005; 283: 2149) "For now the true natural history of today's cases of prostate cancer remains a mystery."

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"In Absolute Terms The Reduction In Mortality Is Moderate. Clinical Decision-Making Will Remain Difficult."

5-9 RADICAL PROSTATECTOMY VERSUS WATCHFUL WAITING IN EARLY PROSTATE CANCER

This article reports estimated 10-year results of a trial comparing radical prostatectomy *vs* watchful waiting **(WW)** in patients with early PC.

Conclusion: Radical prostatectomy reduced disease-specific mortality, overall mortality, local progression. and the risks of metastatic disease. But, PC-specific mortality was reduced by only 5%, and there was no benefit in men over age 65.

STUDY

1. Randomized ~ 700 men (mean age 65; mean PSA = 13) with early PC to: 1) radical surgery, or
   2) watchful waiting.
2. All were under age 75. All had an estimated life expectancy greater than 10 years. Bone scans were negative.
   All were newly diagnosed by cytology or histology and were untreated.
   All had a tumor stage T1b, T1c, or T2 (well differentiated or moderately well differentiated).
      T1b: Incidental histological finding in more than 5% of resected tissue.
      T1c: Tumor identified by needle biopsy performed because of elevated PSA.
      T2: Palpable tumor confined within the prostate. (About ¾ of this cohort had stage T2.)
   (Note—the majority of patients had palpable cancers. (T2) Digital rectal examination is still a valid screen.)
3. Gleason scores:

2 to 4	13%
5 to 6	47%
7	23%
8 to 10	5%.

   (Note, most were in the grey zone noted in the preceding study. This study did not separate outcomes according to Gleason scores.)
4. Primary end-point = death due to PC. Follow-up = up to 10 years.

RESULTS

1. Cumulative incidence at 10 years:	Surgery (%)	WW (%)	Absolute difference (%)	NNT
Disease-specific mortality	9.6	14.9	5.3	19
Distant metastases	15.2	25.4	10.2	10
Local progression	19.2	44.3	25.1	4
2. Disease specific survival at 10 y	91%	86%		

Note that 45% of the surgery group were not cured [10% died; 15% had metastases; 20% local progression]. 15% of the WW group had no evidence of disease at 10 years

The larger reduction in local progression and metastatic disease in the surgery group might be related to fewer symptoms and greater survival after 10 years.

4. "We found that the reduction in disease-specific mortality as a result of radical prostatectomy was . . . *limited to patients younger than 65 years."* But this observation had limited interpretability because it was based on small numbers of patients.

DISCUSSION

1. The absolute benefit of surgery in disease-specific mortality after 10 years was statistically significant (90% of the surgery group survived vs 85% in the WW group), but the difference was a meager 5%.
2. Surgery also reduced the likelihood of local progression and metastatic disease. (This may herald a further lowering of the risk of death due to PC in the surgery group, and development of more troublesome symptoms in the WW group.) But, surgery leads to more immediate side effects (incontinence and impotence). This should be weighed against the increasing incidence of symptoms associated with WW.
3. Benefit from surgery in this study was limited to those under age 65. At 10 years mortality from PC *vs* WW did not differ in men over age 65,
4. The number of patients needed to treat with surgery to achieve one cure may be high.
5. The lead time to onset of symptoms and treatments in WW patients may be long. (*This prolongs anxiety and causes great inconvenience to both patient and family.) After 10 years. . .* "In absolute terms the reduction in mortality is moderate. Clinical decision-making will remain difficult."
7. "A reevaluation of the costs and benefits of radical prostatectomy in the era of widespread screening is necessary."

NEJM May 12, 2005; 352: 1977-84 Original investigation, first author Anna Bill-Axelson, University Hospital Uppsala, Sweden

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Aggressive And Effective Relief Of The Acute Pain May Reduce The Risk Of Chronic Pain.

5-10 POSTHERPETIC PAIN: WHEN SHINGLES WANES, BUT PAIN DOES NOT

This article reports some of the news generated at a recent meeting of the American Pain Society.

Treatment and prevention of chronic neuropathic pain **(CNP)** is a challenge and a research area of great interest. CNP is associated, not only with the post-herpetic state, but with diabetic neuropathy, HIV neuropathy, phantom limb pain, and mastectomy pain. Pain may last for years.

Chronic pain after many kinds of surgery is much more prevalent than has been recognized. The potential for chronic pain should be considered as patients undergo postoperative recovery. Intense pain itself does damage to the nervous system that can be long-lasting. Psychological effects also play a potentially important role.

The varicella-zoster virus damages the peripheral nervous system and the central nervous system. Patients who develop postherpetic neuralgia **(PHN)** have greater damage and loss of peripheral nerve fibers compared with patients who have shingles but do not develop it. The intensity of the acute pain shortly after onset of shingles is a robust predictor of CNP. This leads to the tantalizing hypothesis that aggressive and effective relief of the acute pain may prevent, or at least reduce, the risk of chronic pain.

Acute herpes zoster **(HZ**; shingles) is treated with antiviral drugs in patients over age 50 who are seen within 72 hours of rash onset. These drugs are essential for treating acute pain and reducing postherpetic neuralgia. They are not enough. Oral opioid analgesics, in conjunction with antiviral drugs are likely candidates to decrease the incidence of PHN. They are also more effective in treatment of the acute pain. Opioids are relatively well tolerated by elderly patients. (HZ is a disease of the elderly.)

Ten years ago, the chickenpox vaccine became available for immunization of children. It has done wonders for reducing incidence of chickenpox. As a side-effect, it may actually *increase* prevalence of herpes zoster in adults. This is because, as the prevalence of chickenpox falls in children, adults are less exposed to the virus, and thus lose the booster effect they may receive from exposure to children with the active disease.

JAMA May 25, 2005; 293: 2459-60 “Medical News and Perspectives” reported by Tracy Hampton, JAMA Staff

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