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HIGHLIGHTS AND *EDITORIAL COMMENTS* JULY 2004

7-1 ASSOCIATION BETWEEN CHILD AND ADOLESCENT TELEVISION VIEWING AND ADULT HEALTH.

Watching TV in childhood and adolescence has been linked to adverse health outcomes.

This study explored the long-term health effects of childhood TV viewing.

Mean weekday viewing hours varied between 1.9 hours at age 5 to 3.9 hours at age 13. Ages 5-15 61% of subjects averaged more than 2 hours of TV on weekdays.

Adolescent TV watching correlated with lower childhood socio-economic status, increased parental smoking,, higher maternal and paternal BMI, and higher BMI at age 5.

Childhood and adolescent TV viewing predicted (at age 26) a higher BMI, lower VO_2 max, higher cholesterol, and increased smoking:

Several childhood behaviors could explain the relation between TV viewing and health. The most obvious are physical activity and diet. Watching TV could affect fitness and obesity by displacing time which would be spent on more active pursuits. TV viewing may influence cigarette smoking.

Viewing habits established in childhood may persist into early adulthood.

"We believe that reducing television viewing should become a population health problem."

Excessive viewing might have long-lasting adverse effects on health.

What else can I say? RTJ

7-2 EFFICACY OF MRI AND MAMMOGRAPHY FOR BREAST CANCER SCREENING IN WOMEN WITH FAMILIAL OR GENETIC PREDISPOSITION.

Mammographic screening of women between ages 50-70 can reduce mortality from BC by about 25%. The consensus is that BC screening in this age group is effective. Although screening is frequently offered to women under age 50 who have a genetic predisposition, efficacy is unproven. Preliminary results of screening studies with mammography reported a low sensitivity for detecting BC in these women.

This study compared the efficacy of magnetic resonance imaging **(MRI)** with that of mammography for screening this group of younger, high-risk women (mean age 40).

MRI detected 32 of 45 BCs (22 of these were not visible on mammography). Missed 13 of 45 (including 5 of 6 DCIS, 4 interval cancers, and 1 detected by clinical examination.)

Mammography detected 18 of 45 BCs (10 of which were visible on MRI)' missed 27 (including 22 visible on MRI), but detected more DCIS (5 of 6)

With respect to all BCs:	Sensitivity	Specificity
Clinical examination	18%	98%
Mammography	40%	95%
MRI	71%	90%

In younger women at high risk for BC due to a genetic predisposition or a strong family history, MRI detected more BCs than mammography (71%.*vs* 40%). The specificity of MRI was lower (more false positives—10% vs 5%).

MRI detected 20 cancers that were not detected by mammography or clinical examination. Tumors tended to be smaller and positive nodes were present in only one case.

Comment:

As usual, a test with a high sensitivity (high % of true positive tests) is associated with a lower specificity (high % of false positives). In this group, MRI detected many more BCs than mammography, but the higher false positive rate led to more follow-up examinations and biopsies. Women age 40 have more dense breast tissue. This makes interpretation of mammography more difficult.

I wonder if this study might reduce the frequency of prophylactic mastectomy in high risk women. RTJ

7-3 BREAST CANCER SCREENING WITH MRI: What Are The Data For Patients At High Risk?

The average lifetime risk of BC in American women is one in seven. This risk increases in women with a strong family history of BC, and an inherited mutation (BRCA genes). Women with BRCA mutations make up about 5% to 10% of women with BC. Their risk of ovarian cancer is also high.

Cumulative risk of BC of women with these mutations range from 3% at age 30, to 50% by age 50, and to 85% at age 70. These BCs often occur at a younger age, have "pushing margins", a high nuclear grade, and lack estrogen receptors. Cancers in these women grow rapidly.

MRI is highly sensitive in detecting BC. Disadvantages include cost, variations in technique and interpretation, imperfect specificity, and variations in enhancement during the menstrual cycle (midcycle is optimal). MRI screening will likely be refined and standardized. "Whether the excellent results reported can be achieved in primary care practice remains to be determined."

Discovering and removing a BC in these high risk women does not end surveillance. Screening the remaining breast tissue must continue after surgery. Considering the lifetime need of frequent screening and the continuous anxiety associated, I can understand that many women would grow weary and opt for bilateral prophylactic mastectomy RTJ

7-4 PREOPERATIVE PSA VELOCITY AND RISK OF DEATH FROM PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

This study assessed whether the PSA velocity during the year before the diagnosis of PC could identify those at higher risk for death from PC after radical prostatectomy.

Men whose PSA increased by more than 2.0 ng per mL (*vs* an increase of less than 2.0) during the year preceding the diagnosis of PC had a higher relative risk of dying from PC despite undergoing radical prostatectomy. (RR = 25)

An annual velocity over 2.0 was significantly associated with advanced pathological stage, and high-grade disease. Five % of men with an annual velocity over 2.0 had positive lymph nodes, as compared with 0.7% in men with velocity 2.0 or less.

"Watchful waiting may not be the best option" in men with higher velocities. However, whether these men would have a higher and faster rate of death from PC if they were treated with watchful waiting rather than with radical prostatectomy is not known. This awaits a randomized trial.

The initial Gleason score, clinical tumor stage, and PSA level at diagnosis also are important determinants of risk of death from PC.

PSA may fluctuate over time. This may be due to a "natural" variation, or to differences in and between laboratories. We must be assured that the laboratory produces reliable and reproducible results. It would be well to repeat an outlying PSA.

How can we apply the information from this essentially retrospective study to practicalities of primary care? This is not easy. Primary care patients are rarely followed by PSA determinations made every 6 months. The "length time" between determinations is usually much longer. Still, I believe, it would be well to consider a possible developing PC in a man whose PSA is rapidly rising. The cut point of 2.0 ng per mL/year is arbitrary.

A high initial PSA (confirmed) would also lead to consideration for biopsy. (The cut points are also debatable.) The usually stated cut point of 4.0 ng/mL is not reassuring. A cut point of 2.5 has been recommended for younger men. The Mayo Clinic cites an increase in "normal" range as age progresses. See the internet link cited below.

"Few issues are as controversial" as screening for PC. All men considered for screening should be fully informed about risks as well as benefits of screening and then asked to make up their own minds. It is a mistake for primary care clinicians to add a PSA determination to the routine battery of screening chemical tests without informing the patient.

The U.S. Preventive Services Task Force concludes:

> *The evidence is insufficient to recommend for or against routine PSA screening. There is good evidence that PSA can detect early-stage PC. There is mixed and inconclusive evidence that early detection improves health outcomes Screening is associated with important harms.*

I believe older men and men with co-morbidity which would limit life span to 10 years or less should not be screened.

Many younger men do opt for screening. The object is to detect localized PC at a time when cure is possible. In younger men who have no nodules and who are screened periodically, an increased PSA velocity (or doubling time) as well as a high (and confirmed) initial PSA level would be a consideration for biopsy. There is still no precise answer to the implied question—"When both the patient and the physician agree that the potential adverse effects of treatment exceed the benefits, watchful waiting is an option for managing localized prostate cancer." The track record of the consultant surgeon who will do the radical prostatectomy is important consideration. RTJ

7-5 PROGRESS TOWARD IDENTIFYING AGGRESSIVE PROSTATE CANCER

A substantial proportion of men in the age group most affected by PC die of other causes. Yet the rate of death from PC remains high. (In the USA, 82 men die of PC every day.) Evidence of tumor outside the gland and biochemical relapse may be indicative of incurable disease, but are *not* necessarily predictors of death from PC. A considerable proportion of cancers diagnosed by screening are indolent and non-lethal, and otherwise would not have been detected during the patient's lifetime. In such men, treatment-related complications could exceed disease-related complications.

The rapidly growing body of information regarding the predictive value of PSA velocity (and PSA doubling time) suggests that this approach will become critical in predicting PC-specific survival. In the editorialist's experience, patients with biochemical relapse after prostatectomy, the Gleason score, the time to relapse, and the PSA doubling time all independently predict the probability of distant metastases, and might be an indication for early adjunctive treatment. The PSA doubling time overrides the other variables. The 10-year cancer-specific survival was 93% among patients with a PSA doubling time of more than 10 months, and 58% among those with a doubling time of less than 10 months.

I have tried to think through some guidelines for PSA screening applicable to primary care. This is a personal appraisal. Urologists and other experts may have a different approach.

I believe clinicians may legitimately ask suitable patients if they wish to be screened, while deterring others who might seek a PSA screening, and not even mentioning screening to others.

A. Who should we <u>not</u> screen with PSA

Men who are not beforehand fully informed about ultimate risks as well as possible benefits. (PSA should not routinely be included in the biochemical screen in men who come for a "check up".)

Older men and men with co-morbidity whose life expectancy is less than 10 years.

Men who would not be willing to undergo radical prostatectomy or radiation if indicated.

B. Who should we screen with PSA?

Only men who are fully informed about ultimate risks as well as benefits of screening

Only men with a quality life expectancy over 10 years. (This would tilt screening toward younger, healthier men.)

Only men who would be willing to undergo a radical prostatectomy or radiation if indicated.

C. How often should we screen?

This depends on the patient's degree of concern, and the doctor's willingness to comply with the concerns.

Once a year could be considered reasonable unless an upward trend is suspicious.

D. When should we advise prostate biopsy?

When initial PSA is high for patient's age.

When the PSA velocity over time is increasing rapidly.

When a suspicious nodule is discovered on DRE. (This now becomes a diagnostic procedure, not a screen.)

E. If cancer cells are found, when should radical prostatectomy be advised?

Gleason score 6 and over.

High initial PSA level.

High PSA velocity or short-time doubling

Nodule present

For younger men. In younger men, I believe definitive therapy is almost always indicated.

They are more at risk because they have more time to develop extension of PC. And a greater risk of developing a more aggressive tumor later in life.

F. If cancer cells are found, when should prostatectomy <u>not</u> be advised? (In favor of "watchful waiting"[a].)

In older men:

With significant co-morbidity and a limited life expectancy

With a Gleason score under 6

With a low PSA

No nodule present

Slow PSA velocity

*(**a** I am not sure what "watchful waiting" means. Watch for what? Perhaps advising early adjuvant therapy if extension occurs.)*

I believe the opening statement of the preceding study is a key determinant. "When both the patient and the physician agree that the potential adverse effects of treatment exceed the benefits, watchful waiting is an option for managing localized prostate cancer." This is a judgment call by both. Patient preference is important.

The purpose is to detect and treat while cure is possible and to extend quality life. RTJ

7-6 PHARMACOLOGICAL MANAGEMENT TO REDUCE EXACERBATIONS IN ADULTS WITH ASTHMA

Exacerbations are one of the most important endpoints for clinical trials of asthma. They represent the period of greatest risk of emergency visits, hospitalization, and death.

Corticosteroids are potent (but nonspecific) anti-inflammatory agents. Inhaled corticosteroids (**ICS**) are the single most effective therapy for adult patients with asthma who require more than an occasional inhalation of a short-acting beta agonist. Low doses are first-line therapy. Since airway inflammation is present even in mild disease, inhaled corticosteroids are first-line treatments of patients who need more than an occasional inhalation of short-acting beta agonists. Higher doses (with or without an added long-acting beta-agonist) can be added. With long-term therapy, risk of adverse effects increases. Proper inhaler technique, use of a spacer, and mouth rinsing after each actuation significantly reduce systemic absorption. Patients should be so educated.

By themselves, long-acting inhaled beta agonists have only a modest beneficial effect in reducing exacerbations. When added to inhaled corticosteroids, they do help to reduce exacerbations. Monotherapy is best avoided. It its less effective than ICS.

Lifestyle management leads to the use of a minimal amount of medication: smoking cessation, eliminating allergens, weight loss if overweight or obese (this has been demonstrated to reduce symptoms and improve lung function and quality-of-life in patients with asthma). If smoking continues, oral corticosteroids do not lead to significant improvement.

Oral corticosteroids, leukotriene modifiers, and theophylline can occasionally be used as add-on therapy.

The treatment table on page 373 is helpful.

Smokers should be told—"You will not get better unless you stop smoking."

7-7 FUNCTIONAL DECLINE IN PERIPHERAL ARTERIAL DISEASE

Currently, many medical textbooks and review articles report that most persons with peripheral arterial disease **(PAD)** and intermittent claudication experience stabilization or improvement in their symptoms over time. However, symptoms may not correlate with objective measurement of functional decline. It is possible that

patients with PAD reduce their activity to keep leg symptoms in check. Patient-reported improvement or stabilization of leg symptoms may mask PAD-associated functional decline.

This study assessed whether PAD, ankle-brachial index **(ABI),** and specific leg symptoms predict functional decline over 2 years.

Lower baseline ABI values were associated with greater *mean annual* decline in 6-minute walk performance:

Patients with *asymptomatic* PAD at baseline (compared with patients without PAD), had a greater mean annual decline in 6-minute walk performance, and an increased odds ratio for becoming unable to walk continuously for 6 minutes.

Patients with PAD who experienced leg pain at baseline (compared to patients without PAD) had a greater decline in 6-minute walk, and a decrease in usual-pace 4-meter walking velocity.

This challenges standard thinking about the natural history of leg functioning in patients with PAD. In previous studies, most patients with intermittent claudication reported improvement or stabilization of leg symptoms over 5 years, implying a benign course. However, stabilization or improvement of symptoms does not necessarily indicate stabilization or improvement of leg performance.

Clinicians should consider patients with PAD to be at increased risk of functional decline.

The prevalence of PAD among older persons is high and often unrecognized.

PAD is a serious, progressive, and deadly disease. It requires the same primary and secondary prevention measures as for coronary disease.. Smokers may be told "You will not get better until you stop smoking".

7-8 A PRACTICAL AND EVIDENCE-BASED APPROACH TO CARDIOVASCULAR DISEASE RISK REDUCTION: *Secondary Prevention. A check list:*

ABCS OF CARDIOVASCULAR DISEASE RISK MANAGEMENT

A	B	C
Aspirin	Beta blocker	Cholesterol management
ACE inhibitor	BP control	Cigarettes

D	E
Diet and weight	Exercise
Diabetes	Ejection fraction.

I believe checklists are of value to primary care clinicians. Many effective preventive measures are not prescribed when they are indicated.

Most of these applications are also applicable to primary prevention.

I believe aspirin, beta-blockers, ACE inhibitors, statins, and antihypertension drugs are essential components of the list. Full doses may not be needed. Administration can go low and slow. A pill cutter can drastically reduce cost.

Life-style changes mandatory.

My wife and I have found checklists helpful when we go on trips. We have a list of things to do to set the apartment straight before leaving, and a list of things we should not forget to take along. Almost every time, on going through the lists, we note one or two items we have forgotten.

Clinical practice has become so complex, primary care needs more checklists, RTJ

7-9 CALCULATING THE RISK OF DISEASE www.yourdiseaserisk.harvard.edu

A review note in BMJ July 24, 2004; 329: 237 calls attention to an online tool for determining an individual's risk for five of the most important disease groups in the USA (cancer, diabetes, heart disease, stroke, and osteoporosis). It is presented by The Harvard Center for Cancer Prevention, part of the Harvard School of Public Health. It is an expanded version of the center's cancer risk assessment website.

The site is an interactive educational tool that seeks to encourage healthy lifestyles. It questions the inquirer's eating habits, drinking, and exercise, and offers personalized tips for disease prevention.

I accessed this site on August 13, 2004 and completed the heart disease risk evaluation. Individuals can easily and quickly complete the 21 or more questions asked. It includes all components of the Framingham Risk Score except HDL-cholesterol.

In addition it asks for past history of heart disease, family history, waist size, diabetes, 7 different questions about diet and alcohol, vitamin supplements, and exercise.

On completion it presents a colored risk scale (low to high) and places the individual's estimated risk compared with average.

A useful addition is a list of tips on how you can reduce your individual risk. I received 5 different tips to reduce my risk. RTJ

7-10 SERUM ALDOSTERONE AND THE INCIDENCE OF HYPERTENSION IN NON-HYPERTENSIVE PATIENTS

"All known monogenic forms of hypertension in humans can be traced to defects in renal sodium handling."

The potential role of aldosterone in the pathogenesis of essential hypertension is of great interest. No studies have prospectively evaluated the effect of serum aldosterone on the incidence of hypertension.

Do aldosterone levels within the *physiological range* influence the risk of hypertension?

Higher aldosterone levels *within the normal physiologic range* predispose to hypertension. For each quartile increment of serum aldosterone there was a 16% increase in the risk of an increase of an elevation of BP category, and a 17% increase in risk of developing hypertension.

Relative to the lowest quartile of aldosterone, the highest quartile was associated with a 1.6-fold risk of an elevation in BP category and a 1.6-fold risk of developing hypertension. There was a linear increase with each quartile.

"Increasing aldosterone levels within the physiologic range may predispose to hypertension through promotion of sodium retention, potentiation of action of angiotensin II, and impairment of endothelial function."

I abstracted this article as a matter of interest. It has no practical importance at this time. Watch for follow-up studies. Are we beginning to take "essential" out of essential hypertension? RTJ

7-11 METHYLPREDNISOLONE, VALACYCLOVIR, OR THE COMBINATION FOR VESTIBULAR NEURITIS

This study was performed to determine if anti-viral therapy with valacyclovir (*Valtrex* which is rapidly converted to acyclovir) and/or corticosteroids would benefit.

Methylprednisolone alone significantly improved the long-term outcome of peripheral vestibular function. Antiviral therapy did not benefit any more than placebo.

There is good evidence that the major damage in VN is caused by swelling and mechanical compression of the vestibular nerve within the temporal bone. (As is assumed with the facial nerve in Bell's palsy.)

A reduction in swelling due to the anti-inflammatory effect of corticosteroid may explain why these drugs result in improvement.

Some patients (placebo group) apparently improved spontaneously, and about 4 out of 10 treated with methylprednisolone did not improve. Residual symptoms of VN may persist for years.

During their careers, primary care clinicians will likely encounter at least one case of VN. Incidence is about one case per 30 000 population.

Benign paroxysmal positional vertigo is common. Although the pathogenesis is vastly different. I wonder if a trial of short-term corticosteroids might help. RTJ

7-12 ARE OTC STATINS READY FOR PRIME TIME?

This month, the 10 mg dose of simvastatin (*Zocor*) is expected to become available to the general public in the UK without a prescription. The UK government hopes this will make it easier for individuals to acquire a low-cost statin, and will increase use and reduce cardiovascular morbidity and mortality

There are opponents and proponents, both with good reasons.

Four years ago, a similar attempt in the USA failed to achieve OTC status. The FDA did not believe evidence was sufficient that a 10 mg statin could be used safely. However, the FDA is considering reversing this course. The National Lipid Association has received a grant from Johnson and Johnson-Merck to explore the pros and cons of OTC statin availability in the USA.

I wonder if a compromise would be feasible. The doctor writes a note (not a prescription) informing the pharmacy staff that Mr X is a candidate for OTC statin. This would give the clinician and the pharmacist an opportunity to educate the patient about risks as well as benefits. And also to give the clinician the opportunity to check on adverse effects and effectiveness at future consultations.

The note could be presented at time of each purchase. The statin is not displayed on the shelf. It is available and paid for at the pharmacy check-out, not at the check-out for general purchases and other OTC drugs.

I believe a good argument could be made that statins are safer than some drugs now freely available OTC—eg, NSAIDS, aspirin, and all sorts and conditions of "natural" and "alternative" nostrums. RTJ

I would vote in favor of OTC status. RTJ

ABSTRACTS JULY 2004

"Reducing Television Viewing Should Become A Population Health Problem."

7-1 ASSOCIATION BETWEEN CHILD AND ADOLESCENT TELEVISION VIEWING AND ADULT HEALTH.

"Children in developed countries watch a lot of television. Surveys suggest that time spent watching television during childhood and adolescence might even exceed time spent in school."

Watching TV in childhood and adolescence has been linked to adverse health outcomes. There have been no longitudinal studies of childhood viewing and adult health.

This study explored the long-term health effects of childhood TV viewing.

Conclusion: TV viewing in childhood and adolescence was associated with overweight, poor fitness, smoking, and increased cholesterol levels in adulthood.

STUDY

1. Entered over 1000 children born in 1972-73 into a long-term study. They represented a full range of socio-economic status in New Zealand.
2. Assessed participants at regular intervals from age 3 to 26 regarding their television viewing throughout their lifetime.
3. Related health risks to hours of TV watching daily.

RESULTS

1. Mean viewing hours weekdays at different ages for males. (Females had slightly shorter hours):

Age 5	1.9
13	3.9 (peak)
21	3.0
Ages 5-15	2.4

(61% of subjects ages 5-15 averaged more than 2 hours of TV on weekdays.)

2. Adolescent (ages 5-15) TV watching correlated with lower childhood socio-economic status, increased parental smoking, higher maternal and paternal BMI, and higher BMI at age 5.
3. Childhood and adolescent TV viewing predicted (at age 26) a higher BMI, lower VO_2 max, higher cholesterol, and increased smoking:

	Hours of TV viewing ages 5-15:			
	<1	1-2	2-3	>3
Overweight (%)	26	38	45	48
High cholesterol	15	26	30	28
Smoking	28	37	42	48
Poor fitness	20	21	25	30

(My estimates from figure p 259. RTJ)

4. These associations persisted after adjustment for potential confounders such as childhood socio-economic status, BMI at age 5, parental BMI, parental smoking, and physical activity at age 15.
5. In 26-year olds, population-attributable fractions indicate that 15% of raised cholesterol, 17% of smoking, and 15% of poor fitness can be attributed to watching TV for more than 2 hours a day in childhood and adolescence.

DISCUSSION

1. "TV viewing during childhood and adolescence is associated with overweight, poor cardiorespiratory fitness, raised serum cholesterol, and cigarette smoking in early adulthood. However, "any observational study cannot prove a causal association".
2. Several childhood behaviors could explain the relation between TV viewing and health. The most obvious are physical activity and diet. Watching TV could affect fitness and obesity by displacing time which would be spent on more active pursuits. TV viewing may influence cigarette smoking. Although direct advertising of cigarettes is banned in New Zealand, programs frequently show images of smoking during childhood TV time. TV sponsorship of sports by tobacco companies may be an independent risk factor.
3. Viewing habits established in childhood may persist into early adulthood.
4. The American Academy of Pediatrics recommends that parents limit their child's viewing to 1-2 hours a day. Data suggest that less than 1 hour a day would be even better.
5. Adults are likely to obtain health benefits themselves if they lead by example and turn off the TV. "We believe that reducing television viewing should become a population health problem."

CONCLUSION

TV viewing in childhood and adolescence was associated with overweight, poor fitness, smoking, and raised cholesterol in adulthood. Excessive viewing might have long-lasting adverse effects on health.

Lancet July 17, 2004; 364: 257-62 Original investigation, first author Robert J Hancox, Dunedin School of Medicine, University of Otago, New Zealand.

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MRI Screening Contributed To The Early Detection Of Hereditary Breast Cancer In Younger Women

7-2 EFFICACY OF MRI AND MAMMOGRAPHY FOR BREAST CANCER SCREENING IN WOMEN WITH FAMILIAL OR GENETIC PREDISPOSITION.

"The value of regular surveillance for breast cancer **(BC**) in women with a genetic or familial predisposition to breast cancer is currently unproven." Compared with the lifetime risk of Dutch women (11%), the presence of a mutation of the BRCA1 or BRCA2 gene, and a strong family history increase this risk considerably. Onset of BC in these groups often occurs at a younger age. Early diagnosis may decrease the rate of death.

Mammographic screening of women between ages 50-70 can reduce mortality from BC by about 25%. The consensus is that BC screening in this age group is effective. (There is no consensus about the value of screening in women age 40-49.) Although screening is frequently offered to women under age 50 who have a genetic

predisposition, efficacy is unproven. Preliminary results of screening studies with mammography reported a low sensitivity for detecting BC in these women.

MRI is a sensitive method of breast imaging. It is virtually *uninfluenced* by breast density. (Mammography is.)

This study compared the efficacy of magnetic resonance imaging **(MRI)** with that of mammography for screening a group of younger, high-risk women.

Conclusion: MRI was more sensitive than mammography in detecting BC in younger women with an inherited susceptibility.

STUDY

1. Screened and followed over 1900 women (age 25 to 70; mean = 40) considered to have a 15% cumulative lifetime risk of BC due to a family or genetic predisposition:
   358 were carriers of BRCA mutations (very high risk);
   1052 others were considered at high risk due to family history (30-49%),
   499 at moderate risk (15-29%) due to family history.
2. Surveillance included a clinical breast examination every 6 months, and both mammography and breast MRI every year for a median follow-up of 3 years.
3. Compared characteristics of the cancers detected in the 1900 women by MRI, mammography, and clinical examination *vs* cancers reported by two different age-matched control groups.

RESULTS

1. Over the follow-up period of 3 years , 44 invasive BCs; 6 ductal carcinomas in situ (**DCIS**); and 1 lymphoma were diagnosed. The highest rate of detection was 2.7 per 100 women in BRCA carriers.
2. Cancer detection:
   MRI
   Detected 32 of 45 (22 of these were not visible on mammography)
   Missed 13 of 45.
   Mammography
   Detected 18 of 45 BCs (10 of which were visible on MRI), and missed 27 (including 22 visible on MRI)
   Detected more DCIS (5 of 6)

4. With respect to all BCs:	Sensitivity	Specificity
Clinical examination	18%	98%
Mammography	40%	95%
MRI	71%	90%

5. Evaluated discriminating capacity of the imaging methods by generating receiver-operating-characteristic-(**ROC**) curves:
   Area under the curve:
   MRI 0.827

Mammography	0.686
Difference	0.141

6. Tumors were smaller, and fewer patients had positive axillary nodes than in the control groups.

DISCUSSION

1. In younger women at high risk for BC due to a genetic predisposition or a strong family history of BC, MRI detected more BCs than mammography (71%.*vs* 40%). The specificity of MRI was lower (more false positives—10% vs 5%).
2. The ROC curves demonstrated that MRI was significantly better at discriminating between malignant and benign case.
3. MRI detected 20 cancers that were not detected by mammography or clinical examination. Tumors tended to be smaller and positive nodes were present in only one case.
4. Larger tumors were found in women carriers of BRCA than in the other two groups. This suggests that more frequent screening is needed in this group of women.
5. Mammography had a higher sensitivity for detecting DCIS (5 of 6 cases *vs* 1 of 6).
6. "MRI screening did indeed contribute to the early detection of hereditary breast cancer."
7. MRI will generate more false positive tests ("uncertains") which require short-term follow-up—twice as many unneeded examinations vs mammography, and three times as many biopsies.

CONCLUSION

MRI appears to be more sensitive than mammography in detecting tumors in younger women with an inherited susceptibility to breast cancer..

NEJM July 29, 2004; 351: 427-37 Original investigation by the Magnetic Resonance Imaging Screening Study Group, first author Mieke Kriege, Erasmus Medical Center, Rotterdam, Netherlands.

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"Whether The Excellent Results Reported Can Be Achieved In Primary Care Practice Remains To Be Determined."

7-3 BREAST CANCER SCREENING WITH MRI: What Are The Data For Patients At High Risk?

Cancer is detected in 5 to 7 of every 1000 women on their first screen with mammography, and in 2 or 3 more per 1000 who undergo regular screening.

The average lifetime risk of BC in American women is one in seven. This risk increases in women with a strong family history of BC, and an inherited mutation (BRCA genes) Women with BRCA mutations make up about 5% to 10% of women with BC. Their risk of ovarian cancer is also high.

Cumulative risk of BC of women with these mutations range from 3% at age 30, to 50% by age 50, and to 85% at age 70. These BCs often occur at a younger age, have "pushing margins", a high nuclear grade, and lack estrogen receptors. Cancers in these women grow rapidly.

Strategies for prevention of BC in these women include: bilateral prophylactic mastectomy, chemoprevention, and close surveillance (including yearly mammography beginning at age 25 to 35). However, screening mammography detects less than half of the BCs, perhaps owing to a greater breast tissue density of younger women, or to pathological features of the tumor.

MRI provides information about tissue vascularity that is not available by mammography. (In part due to injections of gadolinium to enhance the tumor's vascularity.)[a] MRI is highly sensitive in detecting BC. Disadvantages include cost, variations in technique and interpretation, imperfect specificity, and variations in enhancement during the menstrual cycle (midcycle is optimal). MRI screening will likely be refined and standardized. "Whether the excellent results reported can be achieved in primary care practice remains to be determined."

In the preceding study, the overall detection rate for all BCs (including DCIS) for the whole group was 10 per 1000 woman-years. The highest rate of detection was 27 per 1000 woman-years in those who were carriers of BCA genes.

Many more were detected by MRI than by mammography. BC was diagnosed in these women at a younger age (30-39). Their BCs were more invasive, and had a high nuclear grade. More were estrogen-receptor negative. Conversely, more were node-negative.

MRI was associated with more false negatives. This leads to increased costs, more follow-ups, anxiety, benign biopsies.

No data exist for women at normal risk.

NEJM July 29, 2004; 351: 497-500 Editorial by Laura Liberman, Memorial Sloan-Kettering Cancer Center, New York.

a Gadolinium is an element (atomic wt 157). It has "paramagnetic" properties which enhances sensitivity of MRI

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A Prognostic Indicator: Prostatectomy, or Watchful Waiting?

7-4 PREOPERATIVE PSA VELOCITY AND RISK OF DEATH FROM PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

"When both the patient and the physician agree that the potential adverse effects of treatment exceed the benefits, watchful waiting is an option for managing localized prostate cancer." **(PC)**

Today, the majority of men with PC present with a non-palpable tumor (stage T1c). They have come to medical attention because of an elevated prostate specific antigen **(PSA)**

Several studies have found that, when considered alone, the rate of rise in PSA levels—the PSA velocity—before the diagnosis of PC can predict tumor stage, grade, and time to disease recurrence. However, not all men with a recurrence die of PC. Competing causes of death are frequent, especially in cases of PC with a protracted course.

This study assessed whether the PSA velocity during the year before the diagnosis of PC could identify those at higher risk for death from PC after radical prostatectomy.

Conclusion: Men whose PSA increased by more than 2.0 ng per mL during the year preceding the diagnosis of PC had a much higher relative risk of dying from PC despite undergoing radical prostatectomy.

STUDY

1. Compiled pretreatment and follow-up information on over 1800 men who participated in a prospective PC screening study. All were treated with radical prostatectomy with intent to cure (clinically localized PC [a]).
2. Of the 1800, 1095 were included in the study cohort. Median age = 65 years (majority age 60-69; 21% under age 60; 23% over age 69). Median PSA level was 4.3 ng per mL. 43% had a PSA under 4.0.[b] Most had a Gleason score 6 or under.
3. In all subjects, the rate of rise of PSA (PSA velocity) had been determined by measuring PSA at 12 months before surgery, at 6 months before surgery, and immediately before surgery.
4. Also determined the PSA level at diagnosis, the Gleason score, and the clinical tumor stage (by digital rectal examination)
5. Median follow-up = 5 years. (Range up to 10 years).
   None received adjuvant hormonal treatment.
   Measured PSA approximately every 6 months after surgery for evidence of recurrence.
   Disease recurrence was defined as a detectable PSA level (over 0.2 ng per mL) on 2 consecutive measurements.
6. Asked the question—Can PSA velocity determined before surgery predict outcomes?

a The majority were T1c (non-palpable tumor discovered by PSA screening); the rest were mainly T2a (palpable in ½ of one lobe only); a few were T2b and T2c (palpable in over half of one lobe, or in both lobes*.) Once a suspicious nodule is discovered by DRE, PSA determinations become less problematic; biopsy is indicated. RTJ*

b Note the high % of patients below the cutoff point often considered an indication for further investigation. This study considered a level of 2.5 to indicate biopsy.

RESULTS

1. There were 366 recurrences (33%) and 27 deaths (2.5%) from PC during follow-up.
2. 262 men (24%) had a velocity over 2.0 ng per mL per year.
3. Overall rates of death from PC seven years after radical prostatectomy among men with a preoperative PSA velocity over 2.0 ng per mL per year according to tumor stage, PSA levels, and Gleason score.

	Death from PC (%)
Men with PSA velocity over 2.0 ng/mL per year (n = 262)	9.2.% (24 of 262 patients)
Men with PSA velocity 2.0 or under (n = 833)	A fraction of 1% over a median of 5 years (only 3 of 833) [c]
(**c** Note the low risk in this group.)	
Tumor stage at diagnosis	
T1c (n = 181)	2.5

T2a (n = 81)	20.5
PSA level at diagnosis	
10.0 and under (n = 216)	7.1
Over 10.0 (n = 46)	17.7
Gleason score at diagnosis	
6 and under (n = 213)	6.9
7 (n = 34)	15.4
8-10 (n = 15)	28

3. In patients with an annual velocity over 2.0 ng/mL per year before surgery, the time to recurrence was shorter and death from PC was much more likely than in those with a level 2.0 and below. "Therefore, the cutoff point for the PSA velocity that provided the best stratification was 2.0 ng per mL."
4. The PSA level at the time of diagnosis, Gleason score of 8-10, and a clinical stage of T2 also predicted death from PC. (If a nodule due to PC is present, prognosis worsens considerably.)
5. An annual velocity over 2.0 was significantly associated with advanced pathological stage, and high-grade disease. Five % of men with an annual velocity over 2.0 had positive lymph nodes, as compared with 0.7% in men with velocity 2.0 or less.

DISCUSSION

1. The study provided new information regarding the association between the PSA velocity during the year before diagnosis and the PSA level at the time of diagnosis.
2. Seven years after radical prostatectomy with curative intent, men with an annual PSA velocity of more than 2.0 before surgery had substantially higher rates of death from PC than men with a level 2.0 or less.
3. "Watchful waiting may not be the best option" in men with higher velocities. However, whether these men would have a higher and faster rate of death from PC if they were treated with watchful waiting rather than with radical prostatectomy is not known. This awaits a randomized trial.
4. The initial Gleason score, clinical tumor stage, and PSA level at diagnosis also are important determinants of risk of death from PC.

CONCLUSION

Men whose PSA level increased by more than 2.0 ng per mL during the year before the diagnosis of PC may have a high risk of dying from PC despite undergoing a radical prostatectomy. For men with a higher PSA velocity who are otherwise in good health, watchful waiting may not be the best option.

NEJM July 8, 2004; 351: 125-35 Original investigation, first author Anthony V D'Amico, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Mass.

Web sites to inform patients about PSA screening:

www.york.ac.uk/inst/crd/em22b.htm

Screening for prostate cancer Information for men considering PSA tests

Centre for Reviews and Dissemination University of York, UK

www.cnn.com/HEALTH/library/HQ/01273.html

Prostate cancer screening: Know your options

Mayo Clinic

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Who Should Be Screened? Who Should Not Be Screened?

7-5 PROGRESS TOWARD IDENTIFYING AGGRESSIVE PROSTATE CANCER

(*This editorial comments and expands on the preceding study.)*

With the advent of widespread prostate specific antigen **(PSA)** testing, there was a sharp increase in the incidence of age-adjusted prostate cancer **(PC)** as well as the proportion of patients with early stages of the disease at the time of diagnosis. There have been substantial shifts toward the use of radical prostatectomy in younger men, and in men with lower PSA levels and non-palpable lesions. Currently, less than 10% of men have distant metastases at the time of initial diagnosis, and the proportion of patients offered local treatment with curative intent has increased substantially.

A substantial proportion of men in the age group most affected by PC die of other causes. Yet the rate of death from PC remains high. (In the USA, 82 men die of PC every day.) Evidence of tumor outside the gland and biochemical relapse may be indicative of incurable disease, but are *not* necessarily predictors of death from PC. A considerable proportion of cancers diagnosed by screening are indolent and non-lethal, and otherwise would not have been detected during the patient's lifetime. In such men, treatment-related complications could exceed disease-related complications.

The preceding study suggested that determining the PSA velocity enhances the ability to identify men who may require immediate biopsy and treatment, and those who could be candidates for watchful waiting.

The rapidly growing body of information regarding the predictive value of PSA velocity (and PSA doubling time) suggests that this approach will become critical in predicting PC-specific survival. In the editorialist's experience, patients with biochemical relapse after prostatectomy, the Gleason score, the time to relapse, and the PSA doubling time all independently predict the probability of distant metastases, and might be an indication for early adjunctive treatment. The PSA doubling time overrides the other variables. The 10-year cancer-specific survival was 93% among patients with a PSA doubling time of more than 10 months, and 58% among those with a doubling time of less than 10 months.

The preceding study provides evidence that the preoperative PSA velocity predicts the risk of dying of PC, and this, together with other clinical and pathological data, may be used to enhance the identification of aggressive PC. Assessment of PSA dynamics may eventually be the key factor in selecting patients with disease for which expectant management may be suitable.

NEJM July 8, 2004; 351: 180-81 Editorial, first author Mario Eisenberger, Johns Hopkins Medical Institutions, Baltimore MD.

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Inhaled Corticosteroids Still the Best.

7-6 PHARMACOLOGICAL MANAGEMENT TO REDUCE EXACERBATIONS IN ADULTS WITH ASTHMA A Systematic Review And Meta-Analysis

The prevalence of self-reported asthma has increased 74% over the past 2 decades. The number of office visits for asthma has doubled, and asthma-related deaths have increased by 61%. Exacerbations are one of the most important endpoints for clinical trials of asthma. They represent the period of greatest risk of emergency visits, hospitalization, and death.

New pharmacological agents have been introduced to reduce this growing morbidity.

This study asks: What is the long-term effect of these agents in preventing exacerbations?

STUDY

1. Systematic review quantified the long-term effect of: 1) inhaled corticosteroids (**ICS**), 2) long-acting inhaled beta-2 agonists (**L-AIBA**), 3) leukotriene modifiers, and 4) anti-IgE therapies.
2. Included trials that were double-blind, had follow-up periods of at least 3 months, and contained data on exacerbations and forced expiratory volume at one second (**FEV1**). Effects were compared with placebo, short acting beta agonists, and with each other.
3. Determined clinical outcomes and relevant exacerbations in adults with chronic asthma.

RESULTS

1. Inhaled corticosteroids were most effective, reducing exacerbations by 54% compared with placebo or short-acting beta-agonists.
2. Long-acting beta agonists alone, compared with placebo, reduced exacerbations by 25%.
3. Combined inhaled corticosteroids and long-acting beta-agonists achieved a 26% reduction above that achieved by corticosteroid monotherapy. Combination therapy was associated with fewer exacerbations than was increasing the dose of corticosteroids.
4. Leukotriene modifier/receptor antagonists reduced exacerbations by 41% compared with placebo, but were less effective than inhaled corticosteroids.
5. Effects on exacerbations

	Relative risk
Inhaled corticosteroids vs placebo	0.46
Higher doses of corticosteroids vs lower doses (at least two times higher)	0.77
Long-acting beta agonists vs placebo	0.75
Combined corticosteroids + long acting beta agonists vs higher-dose corticosteroids	0.86
Leukotriene modifiers/receptor agonists vs placebo	0.59
Leukotriene modifiers/receptor agonists vs inhaled corticosteroids	1.72

6. Compared with placebo, inhaled corticosteroids had salutary effects on FEV1, improving it by about 330 mL in the first 3 months of therapy. Over 6 months effectiveness fell to 150 mL. “This suggests that the principal salutary effects of inhaled corticosteroids on FEV1 occur within the first 3 months.”

DISCUSSION

1. The heart of asthma pathophysiology is chronic airway inflammation caused by allergic sensitization of airways. It is accompanied by dysfunction of airway smooth muscle cells and infiltration of eosinophiles, mast cells, and T lymphocytes that express T-helper cell cytokines such as interleukins.
2. Airway remodeling is another characteristic: smooth muscle hypertrophy, thickening of basement membranes, increased mucus production, and denudation of airway epithelium.
3. Corticosteroids are potent (but nonspecific) anti-inflammatory agents. As such, they appear to be the therapy most effective in controlling asthma symptoms and improving lung function.
4. Since airway inflammation is present even in mild disease, inhaled corticosteroids are first-line treatments of patients who need more than an occasional inhalation of short-acting beta agonists.
5. In patients with moderate to severe airflow impairment, higher-dose therapy with corticosteroids appear to produce greater beneficial effects on risk of exacerbations.
6. What about potential adverse effects of inhaled corticosteroids? In a dose-dependent manner, inhaled corticosteroids have been associated with bone demineralization, osteoporosis, hip fractures, cataracts, glaucoma, skin bruising, and adrenal suppression. The clinical trials examined in this study were too short and underpowered to determine adverse effects.
7. Proper inhaler technique, use of a spacer, and mouth rinsing after each actuation significantly reduce systemic absorption. Patients should be so educated.
8. It is not clear whether the provision of inhaled corticosteroids to patients who are taking oral corticosteroids after hospitalization or emergency room visits reduces the risk of relapse. However, once oral therapy is discontinued, patients should receive inhaled corticosteroids.
9. By themselves, L-AIBA have only a modest beneficial effect in reducing exacerbations. When added to inhaled corticosteroids, they do help to reduce exacerbations. Monotherapy with L-AIBA is best avoided because it its less effective than ICS.
10. The precise role of monoclonal anti-IgE therapy is not clear. It cannot be routinely recommended.
11. Lifestyle management leads to the use of a minimal amount of medication: smoking cessation, eliminating allergens, weight loss if overweight or obese (this has been demonstrated to reduce symptoms and improve lung function and quality-of-life in patients with asthma). If smoking continues, oral corticosteroids do not lead to significant improvement.
12. Severity ranges from mild intermittent to severe persistent. Depending on severity and frequency of day and night symptoms, FEV1, and variability of peak expiratory flow, medication is suggested for each of the 4 grades of severity (p 373):

Step 1	Step 2	Step 3	Step 4
Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
No daily medication	Low-dose inhaled	Low-to medium inhaled	High dose inhaled

needed. Systemic corticosteroids for infrequent exacerbations Intermittent inhaled beta agonists	corticosteroids	corticosteroids + long-acting beta-agonist. Increase dose of inhaled corticosteroids if recurrence is severe Leukotriene modifier or theophylline may be added	corticosteroid + long-acting beta-agonist. Add oral corticosteroid if needed

CONCLUSION

Inhaled corticosteroids are the single most effective therapy for adult patients with asthma who require more than an occasional inhalation of a short-acting beta agonist. Low doses are first-line therapy. Higher doses (with or without an added long-acting beta-agonist) can be prescribed. But long-term high-dose brings the risk of adverse effects.

Leukotriene modifiers/receptor blockers are a reasonable therapy for those who cannot take ICSs.

JAMA July 21, 2004; 929: 367-76 "Clinical Review", original investigation, first author Don D Sin, St Paul's Hospital, Vancouver, British Columbia, Canada.

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PAD Is A Progressive Disease

7-7 FUNCTIONAL DECLINE IN PERIPHERAL ARTERIAL DISEASE

Currently, many medical textbooks and review articles report that most persons with peripheral arterial disease **(PAD)** and intermittent claudication experience stabilization or improvement in their symptoms over time. However, symptoms may not correlate with objective measurement of functional decline. It is possible that patients with PAD reduce their activity to keep leg symptoms in check. Patient-reported improvement or stabilization of leg symptoms may mask PAD-associated functional decline.

This study assessed whether the ankle-brachial index **(ABI),** and specific leg symptoms predicted functional decline over 2 years.

Conclusion: Baseline ABI and the nature of leg symptoms predicted the degree of functional decline.

STUDY

1. Prospective cohort study entered over 650 patients (mean age 71) with and without PAD.
2. Defined PAD as an ABI less than 0.9. ABI was measured by a hand-held Doppler probe. Used an appropriately sized BP cuff to determine systolic pressures in the brachial arteries and foot arteries.
3. Baseline characteristics (means)

	With PAD (n = 417)	Without PAD (n = 259)
ABI	0.65	1.1
Pack years smoking	38	18
Diabetes	31%	20%

Cardiac or cerebrovascular disease	58%	37%

4. Compared baseline function with function at 2 years.

RESULTS

1. Lower baseline ABI values were associated with greater *mean annual* decline in 6-minute walk performance:

ABI under 0.5	- 73 feet
ABI 0.5 to under 0.9	- 59 feet
ABI 0.9 to 1.5	-13 feet

2. Compared with patients without PAD, those with *asymptomatic* PAD at baseline had a greater mean annual decline in 6-minute walk performance (- 9 feet vs -77 feet). And an increased odds ratio for becoming unable to walk continuously for 6 minutes (OR = 3.6).
3. Compared to patients without PAD, those with PAD who experienced leg pain on exertion and at rest at baseline had a greater decline in 6-minute walk (-9 feet vs - 111 feet). And a decline usual-pace 4-meter walking velocity.

DISCUSSION

1. Participants with a low ABI at baseline had significantly greater decline in walking endurance at a 2-year follow-up compared with those with normal baseline ABI.
2. Those with ABI less than 0.5 at baseline (relative to those with ABI 1.1 to 1.5) had a nearly 13-fold increased risk of becoming unable to walk for 6 minutes continuously 2 years later.
3. Baseline leg symptoms among patients with PAD predicted rates of functional decline. Those with leg pain on exertion and/or at rest experienced greater declines in walking endurance and in walking speed than did patients without PAD.
4. This challenges standard thinking about the natural history of leg functioning in patients with PAD. In previous studies, most patients with intermittent claudication reported improvement or stabilization of leg symptoms over 5 years, implying a benign course. However, stabilization or improvement of symptoms does not necessarily indicate stabilization or improvement of leg performance.
5. Clinicians should consider patients with PAD to be at increased risk of functional decline. An ABI under 0.5, and leg pain on exertion and/or at rest are associated with greater functional decline.
6. The prevalence of PAD among older persons is high and often unrecognized.
7. Patients with asymptomatic PAD who develop leg symptoms are particularly likely to have undergone functional decline. If one waits until the patient becomes symptomatic to screen for PAD, additional functional decline will occur prior to the detection of PAD.
8. It is important to note that about 5% of patients with PAD will have an ABI greater than 0.9—a spuriously high ABI due to calcification of lower extremity arteries.

CONCLUSION

Baseline ABI and the nature of leg symptoms predict the degree of functional decline over time.

JAMA July 28, 2004; 292: 453-61 Original investigation, first author Mary McGrae McDermott, Northwestern University Freiberg School of Medicine, Chicago.

7-8 A PRACTICAL AND EVIDENCE-BASED APPROACH TO CARDIOVASCULAR DISEASE RISK REDUCTION: ***Secondary Prevention A Check List***

A wide variety of practice patterns exist for management of patients with coronary artery disease **(CAD).** Implementation of risk-reducing practices remains suboptimal. The treatment gap in secondary prevention (*and primary*) of cardiovascular disease **(CVD)** has become a major challenge in health care,

This review, based on clinical trials, summarizes key studies that guide an evidence-based approach to secondary prevention. It presents a simple check list based on an "ABCDE" format.

ABCS OF CARDIOVASCULAR DISEASE RISK MANAGEMENT

A	B	C
Aspirin	Beta blocker	Cholesterol management
ACE inhibitor	BP control	Cigarettes

D	E
Diet and weight	Exercise
Diabetes	Ejection fraction.

FOR SECONDARY PREVENTION OF CVD

(My adaptation for primary care. RTJ)

A

1. Aspirin (75 mg daily)

   Meta-analyses have reported a reduction in vascular mortality by15% and CVD events by 30%

2. Clopidogrel (*Plavix* 75 mg daily)

   Patients with an acute coronary syndrome, especially if they undergo percutaneous coronary intervention, should be given combined aspirin-clopidogrel for 1 year.

3. Angiotensin-converting enzyme inhibitors:

   A. Patients with heart failure. And patients with left ventricular systolic dysfunction (LVSD) and recent myocardial infarction.

   B. Patients with CVD and/or diabetes as long as the systolic BP is greater than 120 mm Hg

   C. High risk patients without LVSD. (History of vascular disease, or diabetes + one additional risk factor. (Watch for cough and hyperkalemia.)

4. Angiotensin receptor blockers:

   Primary therapy only in patients who cannot tolerate ACE inhibitors.

B

Beta Blocker

For BP control, heart failure, post MI, left ventricular systolic dysfunction.

Blood pressure control

The optimal agent for lowering BP in patients with CVD has yet to be clearly defined.

Most hypertensive patients will require 2 or more agents to achieve target levels.

Thiazides: Because of low cost, thiazides have been considered a first-line drug.

Beta-blockers:

ACE inhibitors: As noted above.

C

Cholesterol control

Diet:

Low saturated fat; low trans fat; high mono-and unsaturated fats and oils; added plant sterols; low sugar; sugar substitutes for sweetening, high complex carbohydrate; high soluble fiber; one-a-day multivitamin

Statin drug.

Cigarette cessation

D

Diet and weight

Aim for BMI < 25.

Follow food pyramid and Mediterranean diet.

Diabetes

Diet; weight loss; metformin a first drug.

E

Exercise

30 minutes a day

Ejection fraction—determine in patients with heart failure. Is it systolic or diastolic?

Salt restriction

Diuretics

Beta-blockers. Start low; go slow.

ACE inhibitors

Effective secondary prevention of CVD is attainable and necessary. Patients with CVD can be expected to take as many as 5 or more drugs to achieve optimal risk reduction. Compliance, cost, drug-drug interactions are impediments. “Most CV risk-reducing strategies have been found to be both medically justified and cost effective.”

Archives Int Med July 26, 2004; 164: 1490-1500 Review Article, first author Ty J Gluckman, Johns Hopkins School of Medicine , Baltimore, MD.

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7-9 CALCULATING THE RISK OF DISEASE www.yourdiseaserisk.harvard.edu

A review note in BMJ July 24, 2004; 329: 237 calls attention to an online tool for determining an individual's risk for five of the most important disease groups in the USA (cancer, diabetes, heart disease, stroke, and osteoporosis). It is presented by The Harvard Center for Cancer Prevention, part of the Harvard School of Public Health. It is an expanded version of the center's cancer risk assessment website.

The site is an interactive educational tool that seeks to encourage healthy lifestyles. It questions the inquirer's eating habits, drinking, and exercise, and offers personalized tips for disease prevention.

BMJ July 24, 2004; 329: 237 "Review" by Giulio Bognolo, BMJ Staff.

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Are we beginning to take "essential" out of essential hypertension?

7-10 SERUM ALDOSTERONE AND THE INCIDENCE OF HYPERTENSION IN NON-HYPERTENSIVE PATIENTS

Primary hyper-aldosteronism is a well-known cause of secondary hypertension.

"All known monogenic forms of hypertension in humans can be traced to defects in renal sodium handling." The potential role of aldosterone in the pathogenesis of essential hypertension is of great interest. No studies have prospectively evaluated the effect of serum aldosterone on the incidence of hypertension.

This study asks: Do aldosterone levels within the *physiological range* influence the risk of hypertension?

Conclusion: Higher aldosterone levels *within the normal physiologic range* predispose to hypertension.

STUDY

1. Investigated the relation of baseline serum aldosterone levels to increases in BP and the incidence of hypertension over 4 years in a cohort of over 1650 community-dwelling non-hypertensive patients (mean age 55). . None had hypertension. Mean BP = 119/73.[a]
2. Measured serum aldosterone levels at baseline, and divided levels into quartiles.
3. Measured BP at 4 years. Defined an *increase* in BP as an increment of at least one BP category as defined by the National Committee[b] And hypertension as a systolic BP of 140 or higher, a diastolic of 90 or higher, or the use of antihypertension drugs.
4. Determined changes in BP related to baseline aldosterone levels

a I combined men and women

b The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines BP as optimal (< 120/80); normal (120-129/80-84); high-normal (130-139/85-89); and hypertension 140/90 and above.

RESULTS

1. Aldosterone levels and incidence of BP outcomes at four years.

	Mean baseline aldosterone ng/dL	Mean baseline BP	Increase in BP (%)	Hypertension (%)
Lowest quartile	5.5	120/72	29	12
Second	8.5	119/73	33	15
Third	11.3	119/73	35	16
Highest	19	117/73	38	17

2. For each quartile increment of aldosterone there was a 16% increase in the risk of an elevation of BP category, and a 17% increase in risk of developing hypertension.
3. Relative to the lowest quartile of aldosterone, the highest quartile was associated with a 1.6-fold risk of an elevation in BP category and a 1.6-fold risk of developing hypertension. There was a linear increase with each quartile.

DISCUSSION

1. Prehistoric humans consumed a sodium-restricted, fruit-and-vegetable diet rich in potassium. The obligatory loss of sodium through sweating in an arid environment and the possibility of catastrophic volume losses due to diarrhea or hemorrhage necessitated the evolution of physiological mechanisms for sodium and water conservation and potassium excretion— the renin-angiotensin-aldosterone system**. (R-A-A-S)**
2. It is not clear whether humans have biologic feedback mechanisms to lower aldosterone levels in the face of the high salt intake prevalent in our society. It is conceivable that an adaptive response essential for survival in a low-sodium environment could turn maladaptive in contemporary society.
3. An enormous body of evidence links dietary sodium intake to BP levels and hypertension.
4. This study tested the possibility that variations in serum aldosterone levels may contribute to the risk of hypertension. The serum level was directly related to the BP outcomes, and increased risk of hypertension.
5. Increased risks of developing hypertension and an increase in the level of BP were evident especially among participants whose serum aldosterone level was in the 4^{th} (highest) quartile relative to those whose level was in the first quartile.
6. Increasing aldosterone levels within the physiologic range may predispose to hypertension through promotion of sodium retention, potentiation of action of angiotensin II, and impairment of endothelial function.

CONCLUSION

In a community based population, increased aldosterone levels within the physiologic range predisposed to development of hypertension.

NEJM July 1,2004; 351: 33-41 Original investigation, first author Ramachandran S Vasan, National Heart, Lung, and Blood Institute, Framingham Heart Study, Framingham Mass.

An editorial in this issue of NEJM (pp 8-10) first author Robert G Dluhy, Harvard Medical School, comments and expands on the study.

There are two primary regulators of aldosterone (the sodium-retaining, potassium-excreting hormone) secretion: 1) potassium, and 2) the renin-angiotensin-aldosterone system. (R-A-A-S) The latter is involved in volume homeostasis, High salt intake suppresses the R-A-A-S; low salt has the opposite effect.

Secondary hyper-aldosteronism is a physiologic response to dietary sodium restriction. It promotes renal sodium conservation. In this setting, hyper-aldosteronism has no cardiovascular consequences.

Hyper-aldosteronism emerges as a villain in persons whose dietary salt intake is normal and the production of aldosterone is inappropriately high for the level of sodium intake. This results in excessive sodium retention, potassium wasting, hypertension, and cardiovascular damage.

Defects in the regulatory relationship between the R-A-A-S and aldosterone production occur by two mechanisms:

1) Hyper-aldosteronism due to autonomous secretion of aldosterone by the adrenal cortex secondary to a neoplasm or hyperplasia; and

2) Hyper-aldosteronism due to activation of the R-A-A-S such as that caused by renal artery stenosis.

Traditionally, hypertension in the setting of hyper-aldosteronism has been thought to be due to expansion of extracellular volume, resulting firm excessive renal resorption of sodium.

Recently the hypothesis of the role of aldosterone in the pathogenesis of cardiovascular disease has expanded in two ways:

1) The oft-quoted low prevalence (1%) of hyper-aldosteronism among persons with hypertension has been challenged. Recent studies reported that up to 15% of persons with essential hypertension fulfill the criteria for primary hyper-aldosteronism. Most of these have mild serum elevations (usually due to idiopathic adrenal hyperplasia). Most do not have hypokalemia. The presence of a normal K does not rule out primary adrenal hyper-aldosteronism.
2) 2) Aldosterone acts on target organs other than the kidney. It induces inflammatory processes, collagen formation, fibrosis, and necrosis. Cardiac and renal damage occur.

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Corticosteroids Benefited; Valacyclovir Did Not.

7-11 METHYLPREDNISOLONE, VALACYCLOVIR, OR THE COMBINATION FOR VESTIBULAR NEURITIS

Vestibular neuritis **(VN)** is the second most common cause of peripheral vestibular vertigo. (Benign paroxysmal positional vertigo is the most common). It accounts for 7% of patients who present at clinical specializing in treatment of dizziness. Reactivation of herpes simplex virus type 1 infection is an assumed cause, but the evidence of this is circumstantial. Inflammation of the vestibular nerve or labyrinthine ischemia has also been proposed as a cause.

The key signs and symptoms are acute onset of sustained rotary vertigo, postural imbalance with a positive Romberg's sign (falling toward the affected ear when eyes are closed), horizontal spontaneous nystagmus (toward the unaffected ear) with a rotational component, and nausea. Caloric testing (irrigation with warm or cold water) invariably shows ipsilateral hypo-responsiveness or non-responsiveness.

Recovery is usually incomplete. Caloric responses normalize in a *minority* of patients. Postural imbalance persists during walking, and especially during head movement toward the affected ear.

This study was performed to determine if anti-viral therapy with valacyclovir (*Valtrex* which is rapidly converted to acyclovir) and/or corticosteroids would benefit.

Conclusion: Corticosteroids benefited; valacyclovir did not.

STUDY

1. Prospective, randomized, double-blind trial entered 141 patients (mean age 48) with VN, and followed 114 to conclusion . None had tinnitus or acute hearing loss. All started treatment within 3 days of onset of symptoms.
2. Randomized to: 1) methylprednisolone [beginning with 100 mg daily and tapering over 22 days], 2) valacyclovir [two 500 mg capsules 3 times daily for 7 days], 3) both, or 4) placebo.
3. Determined vestibular function by caloric irrigation within 3 days of onset of symptoms and at 12 months.

RESULTS

1. Mean percent Improvement in vestibular function at 12 months:

Placebo	40
Methylprednisolone alone	62
Valacyclovir alone	36
Both	59

2. 77% of methylprednisolone recipients, and 32% of valacyclovir-placebo recipients, had complete or partial recovery of vestibular function.
3. The combination was not superior to methylprednisolone alone.
4. No assessment was made in the period between start of therapy and 12 months.

DISCUSSION

1. Methylprednisolone alone significantly improved the long-term outcome of peripheral vestibular function among patient with VN.
2. Antiviral therapy did *not* lead to improvement despite the assumed viral cause.
3. Bell's palsy has the same pathogenesis as VN. Studies of acyclovir + corticosteroids have demonstrated significantly improved outcomes in Bell's palsy as compared with corticosteroids alone. Results of studies, however, have been contradictory.
4, There is good evidence that the major damage in VN is caused by swelling and mechanical compression of the vestibular nerve within the temporal bone. (As is assumed with the facial nerve in Bell's palsy.)
5. A reduction in swelling due to the anti-inflammatory effect of corticosteroid may explain why these drugs result in improvement.

CONCLUSION

Methylprednisolone significantly improved recovery of peripheral vestibular function in patients with VN. Valacyclovir did not.

NEJM July 22, 2004; 351: 354-61 Original investigation, first author Michael Strupp, University of Munich, Germany.

Comment:

Note that some patients (placebo group) apparently improved spontaneously. About 4 out of 10 treated with methylprednisolone did not improve. Residual symptoms of VN may persist for years.

During their careers, primary care clinicians will likely encounter at least one case of VN. Incidence is about one case per 30 000 population.

Benign paroxysmal positional vertigo is common. Although the pathogenesis is vastly different, I wonder if a trial of short-term corticosteroids might help. RTJ

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Would This Result In A "Dramatic Decline In Myocardial Infarctions In The USA". ?

7-12 ARE OTC STATINS READY FOR PRIME TIME?

This month, the 10 mg dose of simvastatin (*Zocor*) is expected to become available to the general public in the UK without a prescription. The UK government hopes this will make it easier for individuals to acquire a low-cost statin, and will increase use and reduce cardiovascular morbidity and mortality

There are concerns.

While low doses may reduce cholesterol levels, they have not been proven to reduce cardiovascular morbidity of mortality. There are no trials of OTC statins for effectiveness in primary prevention of heart disease. There are no data on compliance with OTC statins. Statins must be taken long-term, increasing the risk of adverse effects.

Expanding statin use to potentially millions of otherwise healthy individuals could mean that thousands will experience myopathy.

Statins may be taken by people who do not need them.

Individuals may lose sight of the need for lifestyle changes if they believe taking a pill will suffice.

Proponents of OTC use argue:

Prescription-only use leads to higher costs and limits use in a large population at risk.

Convenience

Low cost

Use by people with mild elevations of cholesterol who otherwise would not be treated.

A past president of the American Heart Association said he suspects that if individuals with moderately elevated cholesterol levels were to take low-dose statins, in 5 years there would be a dramatic decline in myocardial infarctions in the USA.

Four years ago, a similar attempt in the USA failed to achieve OTC status. The FDA did not believe evidence was sufficient that a 10 mg statin could be used safely. However, the FDA is considering reversing this course. The National Lipid Association has received a grant from Johnson and Johnson-Merck to explore the pros and cons of OTC statin availability in the USA.

JAMA July21, 2004; 292: 317-18 "Medical News and Perspectives", Commentary by Mike Mitka, JAMA Staff.