LITERATURE REVIEW

Prospective Determination of Apolipoprotein E Phenotype, Dementia and Mortality
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The Helsinki Aging Study is an ongoing, prospective, birth cohort study. Randomly selected persons aged 75, 80, and 85 were tested with the Clinical Dementia Rating scale (CDR) and MMSE at baseline and at follow-up five years later. Neurological exams and further testing (CT, blood testing, etc.) were performed on anyone with a CDR score ≥ 0.5 (questionable dementia) to determine the presence and cause of dementia: probable Alzheimer's Disease (AD), uncertain AD, or vascular dementia. Apolipoprotein E phenotype (but not genotype) was obtained at baseline in 550 unselected patients and the results were collapsed into two categories: presence or absence of an ε4 allele. Cognitive status, presence or absence of dementia, and mortality and cause of death for those who had died were determined after five years.

There was no significant difference at baseline in the proportion of individuals with an ε4 allele in any of the three age groups, nor was ε4 associated with hypertension, myocardial infarction, angina, or peripheral vascular disease. Consistent with previous studies, ApoE ε4 was over-represented in the patients with AD. However, ApoE ε4 was also more common in vascular dementia than in non-demented subjects (Table 1). The positive predictive value for a diagnosis of AD (probable or uncertain) was 14%; the negative predictive value was 95%.

The five-year all-cause mortality for each age group, stratified by presence or absence of ApoE ε4 allele, is shown in Table 2 as percentages, as well as the risk ratio for death. The authors conclude that presence of an ε4 allele is associated with an increased risk of death due to dementia and all-cause mortality in all age groups and that the effect persists at the oldest ages, in contrast to the findings of some prior studies. However, despite the authors' conclusions, while there was no difference in the baseline frequency of ApoE ε4 in the three age groups studied, there was a decreasing association between ε4 and all-cause mortality,

as shown by the decline in risk ratios from the youngest to oldest groups.

This study also indicates that ApoE ε4 is associated with not only AD as a cause for dementia, but with vascular dementia (VaD) as well. While there may have been overlap between the diagnostic categories of the dementia groups, subjects whose clinical findings were consistent with both AD and VaD were classified as AD. Thus, for any VaD subjects mistakenly classified as AD, the net effect would be to strengthen the association between ε4 and VaD and to weaken that between ε4 and AD.

Table 1

Proportion of subjects with ApoE ε4 allele at baseline

Non-demented	24%
AD-probable or uncertain	51%
Vascular dementia	34%

Table 2

Five-year all-cause mortality - % of deaths

	No ε4	ε4	Risk Ratio
75 years (n=182)	17.6	32.6	1.85
80 years (n=185)	34.8	52.8	1.52
85 years (n=183)	58.2	57.1	0.98

Table 3

Predictive Value of e4 allele for AD at Baseline, 5-year Total Mortality, and Death Attributable to Dementia

	Risk Ratio
AD at baseline	3.24
All cause mortality	1.61
Death attributable to Dementia	2.20

LITERATURE REVIEW

Compression-of-Morbidity vs. Increasing Misery In Our Aging Population
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Introduction: The increasing life expectancy of individuals is a function both of healthier living conditions and better medical care for diseases. As people live longer can they expect a longer lifetime period of morbidity with its loss of function, dependence, and misery? Or is there a "compression of morbidity?" Is geriatric disability being compressed into fewer years toward the end of a longer life? The authors of this report conclude that their study supports the hypothesis that increased life expectancy is associated with a compression-of-morbidity.

Study Methodology: This study was based upon review of an unique set of data collected on the health status of individuals attending the University of Pennsylvania in 1939 and 1940. There was a subsequent follow-up survey in 1962 and then, starting in 1986, health-assessment questionnaires were used to obtain information on disability, medical history, and health habits on a near annual basis.

The study population consisted of 1741 indi-

viduals. 77% were male. The population was 99% Caucasian. The mean age in 1986 was 67 (± 2.8 years S.D.).

Variables of interest included age, sex, body-mass index (weight in kg/height in meters squared), smoking habits, exercise, number of chronic conditions, use of medical services, and disability index at time of entry. Chronic conditions included arthritis, back pain, osteoporosis, heart disease, hypertension, stroke, diabetes, cancer, and pulmonary disease.

The annual health-assessment questionnaires since 1986 assessed disability in terms of 8 activities of daily living. A cumulative-disability index was calculated utilizing a methodology well verified by past studies referenced in the report. Minimal disability (a value of 0.1) represented "some difficulty" with dressing, rising, eating, walking, grooming, reaching, gripping, or "performing errands." The average index for someone with rheumatoid arthritis is 1.2 per year. The average index for

someone with osteoarthritis is 0.8 per year.

For analysis, the study population was stratified into low, medium, and high risk groups based upon scores for 3 variables that have well established associations with disability: body-mass index, smoking, and exercise.

Cumulative-disability was estimated as the sum of the annual disability indices from 1986 until the last completed questionnaire before death or until 1994 in the survivors. Cumulative-disability was used as a surrogate measure for total disability.

Results: The subjects in the high-risk group had an average cumulative-disability index of 1.02. The moderate-risk group had an index of 0.71. The low-risk group had an index of 0.49 (P for trend < 0.001). Females had higher disability indices in all risk groups.

Mortality rates differed among the three risk groups: the high-risk 11.9%, moderate-risk 9.9%, and low-risk 7.9%.

The onset of minimal disability (annual index of 0.1) by age was postponed by approximately 7 years in the low-risk group when compared to the high-risk group.

Discussion: The compression-of morbidity hypothesis would predict that the age at time of initial disability will have increased more than the gain in longevity. This results in fewer years of disability at older ages and at a lower level of impairment.

The question of whether improvements in public health and modern medical care is resulting in a compression-of-morbidity has implications for planners of health care policy and for insurers with long-term care insurance products.

The authors concluded that their study supports the compression-of-morbidity hypothesis.

Persons with lower health risks had less disability as measured in a cumulative-disability index. This was seen when adjusted for attained age. In addition, the age of onset of disability was also delayed in low risk individuals.

While supporting the compression-of-morbidity hypothesis, this study raises many interesting questions.

This study is based on Caucasian individuals who attended university during the 1939-1940. The same effects of low-risk health status may not be applicable to a population with a more diverse race and socioeconomic background.

This study is a longitudinal study and ongoing. The individuals studied are relatively young. At entry, they were approximately 67 years old and in 1994 their mean age was 75 years. The question of whether the cumulative lifetime disability will be lower in the low-risk group than in the high risk group was not answered. The health-assessment questionnaire used for this study assessed "activities of daily living" that included the function of "performing errands." The prevalence of cognitive dysfunction increases geometrically in the 8th and 9th decades. The cumulative-disability indices may approach each other if individuals with lower health risks end up living longer lives with disability. Note that the mortality rate in the high-risk group approached twice the rate as in the low-risk group. More individuals in the low-risk group can be expected to reach the 9th decade of life.

The current study does not provide analysis of disease-specific chronic conditions like arthritis, osteoporosis, and back pain. It is the increasing role of these conditions balanced against mortality risks that may or may not shorten the cumulative lifetime burden of a low-risk group compared to those with high risk profiles.

It will be interesting to follow this study in the future.

LITERATURE REVIEW

Increased Cancer Mortality Following a History of Nonmelanoma Skin Cancer
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We see it nearly everyday in medical records, a history of past treatment for basal cell carcinoma. At times I have been heard to murmur, something to the effect that, "He seems young to have had that already", but have usually not given it much consideration beyond that. I know that I, as an underwriter, have gotten very blasé about nonmelanotic skin cancers, even to the point of considering this condition as much a right of passage into older age as acne is to adolescence. This study now shows that I must reconsider that approach.

Methods
The study is the result of the Cancer Prevention Study II which was started in 1982, ran for 12 years of follow-up, and had nearly 1.1 million participants. In this study, any participant who had a previous history of nonmelanotic skin cancer was followed. If there was a death, the cause of death was determined and recorded. Cancer mortality was then compared to those in the study without the preceding skin cancer history. There were 19,102 men and 15,960 women had had a history of nonmelanotic skin cancer at the start of the study.

Results
The results show that over the course of the study (12 years) there were a total of 26,622 male and 21,084 female deaths from all types of cancer. In the study group, i.e. those who had had a previous nonmelanotic skin cancer, the mortality rate was 20% to 30% higher than those participants with no history of skin cancer. The relative risk (RR) for specific cancers were:

- Melanoma: RR, 3.36 in men
  RR, 3.52 in women
- Pharynx: RR, 2.77 in men
  RR, 2.81 in women
- Lung: RR, 1.37 in men
  RR, 1.46 in women
- Non-Hodgkin Lymphoma: RR, 1.32 in men
  RR, 1.50 in women
- Salivary Glands RR, 2.96 men only
- Prostate RR, 1.28

➢ Testis   RR, 12.7
➢ Bladder   RR, 1.41 men only
➢ Leukemia   RR, 1.37 men only
➢ Breast   RR, 1.34 women only

Discussion

The findings presented above have been seen before in several European studies but have not had significant coverage in the United States. As mentioned at the beginning of this article, my personal underwriting practice has been to pay little attention to basal cell carcinomas as a significant predictor of mortality. While it is a fairly easy bridge to understand why there is a three-fold increase in melanoma based on sun exposure as a cause for melanoma and nonmelanoma lesions. For me, it is a more difficult connection to explain the rise in all of these different cancers including the 12-fold increase in testicular cancer. Perhaps these numbers might suggest that the presence of a nonmelanotic skin cancer might herald some underlying defect in that individual to recognize and correct underlying genetic mutations. Perhaps there is more damage from UV exposure than we have ever realized. Whatever the source, the presence of nonmelanotic skin cancer appears to have a significant relationship with other, more virulent, cancers and so deserves more attention in the underwriting process.

LITERATURE REVIEW

Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer

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Prostate cancer continues to be a significant cause of morbidity and mortality. Adenocarcinoma of the prostate has the highest incidence of all cancers in men in the United States. Treatment of prostate cancer has been evolving over the last decade and there are many current controversies in this arena. The role of radical prostatectomy, once the unquestionable standard, has been challenged by less invasive radiation therapy. Implant, or interstitial radiation therapy is the 'new kid on the block'.

There are no prospective, randomized trials comparing definitive local treatment options. There are retrospective trials that look at external beam radiotherapy, radical prostatectomy and outcomes which stratify by risk factors. There are no trials which include implant radiotherapy with external beam radiation therapy and radical prostatectomy which are stratified with pretreatment risk factors.

This study is a retrospective analysis designed to compare the standard radical prostatectomy, and external beam radiation therapy with implant treatment (with or without androgen deprivation). The trial uses freedom from PSA failure as the main outcome measure.

Between 1989-1997, 1872 patients were accumulated who had clinically localized prostate cancer. Of this cohort, 888 received RP, 766 RT, and 218 implant treatment. Clinical staging (AJCC 1992 Staging System) included: history and physical exam, digital rectal exam, PSA, CT or MRI, bone scan, transrectal ultrasound guided biopsy, and Gleason scoring.

Risk groups were identified using three prognostic factors: PSA, Gleason score, and clinical stage. Low risk patients were Stage T1c , T2a, PSA <10 and a Gleason score of <6. This group was expected to have a PSA failure rate of 25% at 5 years.

High risk patients were those with Stage T2c , or PSA >20, or a Gleason score 8 or more. Fail-

ure rates were expected to be at least 50% at 5 years.

The remaining patients; PSA 10-20, or Gleason 7, or Stage T2b were considered to be intermediate risks with a failure rate 25-50% at five years.

Because of the high incidence of urinary incontinence with implant therapy, patients with T1a or T1b were managed with radical prostatectomy or external beam radiation therapy and not included in this study. The definition of a PSA failure required three consecutive rising PSA values measured at least 3 months apart.

Study Results
The low risk group derived equal benefit in all four treatment arms. There was no statistically significant difference in the PSA failure rate at 5 years of follow-up. The addition of androgen deprivation also added no significant benefit to the implant subset.

The intermediate risk group did significantly worse with implant therapy. The small numbers in this group did not allow for evaluation of the difference between implant with AD and RT or RP.

For the high risk group, PSA failure was markedly worse in the implant arms (with or without androgenic deprivation). It is interest-ing to note that there were more favorable factors in the implant group, yet they still fared much poorer.

The authors also plotted the data using Gleason scores alone versus PSA failure rate. Results were similar in that the lower Gleason scores showed no difference in all four arms of treatment. PSA failure rate of the implant treatment(with or without androgenic deprivation) was similar to the RT and RP. The intermediate (Gleason 7) and high risk (Gleason 8 or more) did much poorer with the implant treatment.

The main thrust of this study is to show that implant treatment may offer similar results in low risk patients. Intermediate and high risk patients did not see favorable outcomes as compared with external beam radiation therapy or radical prostatectomy.

Unfortunately the study was retrospective and nonrandomized. The arms with implant treatment were much smaller than the other two. At times the numbers were too small to make meaningful interpretations possible. Unfortunately even with the small number of implant patients, the study attempted to delineate the value of adding androgen deprivation. This study should not be viewed as conclusive, rather as a guide to direct future studies. The next step should be a randomized, prospective study of low risk patients.

LITERATURE REVIEW

The Risk of a Diagnosis of Cancer after Primary Deep Venous Thrombosis or Pulmonary Embolism
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Reviewers Comments
This Danish population-based study demonstrated that there is a significant association of cancer with venous thromboembolism (VTE). Risk varies with duration from the episode. For single episodes the risk is significantly increased only in the first six months after the event. For recurrent episodes of VTE, the risk is significantly increased in the first year after the event and remains marginally but statistically greater than expected in subsequent years. The relative risk of cancer after VTE decreases with age. Certain cancers occur more frequently than expected: cancer of the pancreas, ovary, brain and primary hepatic cancer. While past studies have alternately supported and not supported this association, those studies have been small and not population-based.

Background
This study used population-based data. All persons from the Danish National Registry of Patients with a primary diagnosis of primary

deep venous thrombosis (DVT) or pulmonary embolism (PE) during a hospitalization between January 1, 1977 and December 31, 1992 were reviewed. (The Danish National Registry of Patients records 99.4% of all Danish hospital discharges.) DVT and PE were used only if either was the primary diagnosis. Excluded were cases with surgery within six months, pre-existing cancer, pregnancy, or those with a secondary diagnosis of DVT or PE.

Each patient was followed for the occurrence of cancer from the date of the first hospitalization until the date of death or December 31, 1993. This was accomplished by using the Danish Cancer Registry and the Cause of Death Registry. These registries are supervised by physicians and are considered to be 95 to 98% complete and valid.

Subcohorts were defined by age (age < 60, 60 to 74, and > 74 years) and the presence or absence of a recurrence of VTE (two or more episodes of venous thrombosis or pulmonary

embolism separated by at least three months). Expected cases of cancer were estimated according to sex, age and 5 year calendar periods.

The cohort was equally divided by sex. 33% were below age 60, 37% between age 60 and 74, and 30% age 75 and older. Patients with DVT were followed longer than those with PE (6.1 vs. 3.6 years).

Results

26,600 individuals were studied. 15,348 patients were identified with DVT. In this cohort, there were 1737 cases of cancer with 1372 expected cases, with a standardized incidence ratio (SIR) of 1.3, (95 percent confidence interval, 1.21-1.33) for all time intervals. 11,305 patients were identified with PE. In this cohort, there were 730 observed cases of cancer with 556 expected cases of cancer, with a SIR of 1.3 (1.22-1.44) for all time intervals.

Subcohorts were examined for a difference in risk. By time interval, 0 to <6 months post VTE, the SIR was 3.0 (2.7-3.4) for DVT and 3.0 (2.5- 3.6) for PE; for 6 to < 12 months the risk was marginally increased, and for 12 months up there was no statistically significant increase, with one exception, leukemia had a SIR of 2.5 (1.2 - 4.4).

Both DVT and PE had a SIR of 1.3 for all time intervals. When stratified by time the risk was only significantly elevated during the first six months post VTE and declined rapidly to a constant level of 1.0 at one year post DVT or PE.

A subcort of 3762 patients were identified with recurrent VTE. For either recurrent DVT or PE, the risk of cancer was 3.2 (2.0-4.8) in the first

year post VTE and 1.3 (1.2 - 1.5) over one year. This is in contrast to single episodes of VTE, where the risk was 2.2 (2.0 - 2.4) in the first year and 1.1 (1.1-1.2) over one year.

The SIR for cancer decreased with increasing age. In the first year post VTE, for age < 60 years the SIR was 3.6 (2.9-4.2), for 60 to 74 years the SIR was 2.2 (1.9-2.5) and for > 74 years the SIR was 1.8 (1.6-2.1). Other studies have found the relative risk to be higher at younger ages. No difference in risk was observed with sex. No difference was observed with smoking-related cancers vs. non smoking-related cancers. 40% of the individuals diagnosed with cancer within one year had distant metastases at the time of the diagnosis (of the cancer). Strong associations were observed for cancer of the pancreas, ovary, brain and primary hepatic cancer.

One question addressed is whether the thromboembolic event was causative rather than a result of the cancer. This appears unlikely since the incidence of cancer decreased with increasing time after the event.

The authors made the following conclusion regarding the indication for the evaluation of cancer post VTE: Since most of the cancers were diagnosed in the first year of follow-up, the cancer was likely present at the time of VTE. It would have required an extensive workup to diagnose the cancer. It is unclear if early intervention would have changed the outcome. 26,600 persons would have had to be screened to detect 304 excess cancers. About 40% of the cancers were metastatic at the time of diagnosis of the VTE. Based on these assumptions the authors suggest that only simple methods of screening be employed in patients post primary VTE.