

Table 1 Cell membrane destruction with and without carotenoids

Percentage of stained cells	Cells without β -carotene	Cells with β -carotene	Cells without lycopene	Cells with lycopene
Trypan blue	25.3	7.4	23.6	2.8
Eosin	51.6*	14.6*	74.3*	9.1*
Protection factor	Trypan blue Eosin	3.4 3.5		8.6 8.2

Cell membrane destruction is shown by cell staining with both trypan blue and eosin. All the results ($\pm 20\%$) are based on the mean of at least 10 measurements. The results were corrected for the small percentage of stained cells due to the preparation technique. *The concentration of NN was higher in these experiments.

ponent of polluted air and cigarette smoke, the NO_2 radical, than β -carotene. Thus anti-cancer trials should be extended to lycopene, especially where smokers are involved. Of course, in addition to β -carotene and lycopene, there are many other carotenoids, some of which are used as food colourants. As a marker for future cancer prevention trials, we will

compare the quenching of a wide spectrum of (membrane-damaging) radical species by a range of carotenoids and hence establish an order of priority of carotenoids for intervention trials to inhibit disease.

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The impact of family history on early detection of prostate cancer

To the editor — Prostate cancer is the most frequent cancer in men in North America and is the cause of the second greatest number of deaths from cancer in males¹. Because patient survival is better when prostate cancer is confined to the gland, as opposed to cancer that has spread at the time of diagnosis, and because screen-detected prostate cancer is more often locally confined than clinically detected cancer,^{2,3} it is anticipated that the early detection of prostate cancer will lead to a reduction of mortality from this cancer in the population. Two methods of early detection in current use, and under evaluation as population-based screening tests, are the digital rectal examination and the measurement in blood of prostate-specific antigen (PSA).

A screening test is most likely to be of benefit to groups at highest risk for cancer, especially when the rate of false-positive tests is significant and when there is morbidity associated with follow-up diagnostic testing and treatment. Currently,

criteria that can be used to identify men at high-risk for prostate cancer include age, ethnicity, country of origin and a family history of the disease.⁴

To determine whether family history is associated with an increased prevalence of prostate cancer in an unselected group of men attending a hospital-based screening clinic, we have enquired about affected relatives before prostate cancer screening in 6,390 men, aged 50–80 years, in the Quebec City region. This study was done as part of a prospective study evaluating the impact of screening on prostate cancer mortality (Laval University Prostate Cancer Detection Program)^{3,5}. A total of 26,781 men, aged 45 and above, was selected from the electoral lists and sent a written invitation to participate in the screening project, between 1988 and 1992. Of these, 7,277 (27.2%) indicated their willingness to participate. Subjects were asked to enter an annual screening program designed to evaluate the utility of PSA screening, digital rectal examination and trans-rectal ultrasound imaging

in reducing prostate cancer mortality. The great majority of these men were of French-Canadian ancestry. Before examination and screening, the participants were asked about a history of prostate cancer in a brother, father, uncle or grandfather. The diagnosis of prostate cancer in relatives was based on the subject's recall and was not confirmed by examination of pathology records.

The screening examination consisted of a rectal examination by one of five experienced clinicians and a PSA blood test. PSA was measured by radioimmunoassay (Tandem-R PSA, Hybritech, Inc). Individuals found to have a PSA level above $3.0 \mu\text{g l}^{-1}$, or an abnormal rectal examination were considered to be positive and were recommended to have further evaluation by trans-rectal ultrasound imaging. The examiners noted the size of the prostate, asymmetry or nodularity of the prostatic contour and areas of induration. Transaxial and sagittal scanning of the prostate was performed using a model 1846 Bruel and Kjaer ultrasound appara-

LETTERS TO THE EDITOR

Table 1 The prevalence of prostate cancer and family history

Family history	Number of subjects	Number of cancers	Prevalence (%)	Relative risk (95% CI)	P-value
Brother affected	186	19	10.21	2.62 (1.69, 4.06)	0.0002
Father affected	379	18	4.75	1.22 (0.77, 1.94)	0.70
No first-degree relative affected	5,839	227	3.89	1.00	–
Any first-degree relative affected	552	37	6.70	1.72 (1.21, 2.44)	0.002
Any second-degree relative affected	124	6	4.83	1.24 (0.27, 5.59)	0.59
All subjects	6,390	264	4.13	–	–

The relative risk is calculated with reference to the class of subjects who report no first-degree relative affected. CI, confidence interval. P-values are based on chi-square test. First-degree relatives include brothers, fathers and sons. Second-degree relatives include grandfathers and uncles.

tus using a 7-MHz transducer. A prostate biopsy was performed under ultrasound guidance when a discrete hypoechoic lesion was visualized. Areas corresponding to palpable abnormalities were also subject to biopsies. Biopsies were performed on 50.5% of the men who underwent ultrasound examination. The diagnosis of prostate cancer was confirmed by microscopic examination of the biopsy material.

Of the 6,390 men who underwent screening, 1,563, or 24.5%, had a positive test by either rectal examination or by the PSA test. Of these, 1,261 had a PSA level above $3.0 \mu\text{g l}^{-1}$ (19.7% of total), and 504 had a positive rectal examination (7.9%); 202 men (3.2%) were positive by both criteria. Twenty-six men refused follow-up examination. A total of 264 prostate cancers were identified, representing 4.1% of the 6,390 subjects who entered the study and 34.0% of those who underwent biopsy.

A family history of prostate cancer was reported by 658 men (10.3%). There were 379 men who reported a father with prostate cancer (5.9%), 186 men who reported a brother with cancer (2.9%), and 124 men who reported a grandfather or uncle with prostate cancer (1.9%). Prostate cancer was detected in 10.2% of subjects who reported a brother with prostate cancer. This frequency was 2.62 times greater than for men with no affected first-degree relative (95% confidence interval (CI) 1.69–4.06) (Table 1). The detection rate among those who reported a father with prostate cancer (4.8%) was not significantly greater.

The men who reported a brother with cancer were slightly older at examination (64.2 years) than those who reported no affected first-degree relative (60.9 years; $P = 0.03$). However, this age difference

could not explain the higher frequency of prostate cancer in patients with affected brothers; after adjusting for age at examination by using the Mantel-Haenszel technique⁶, the relative risk was 2.73. The men found to have cancer were on average 5.6 years older than those without cancer (66.3 years versus 60.7 years). There was only a small difference in the age of diagnosis of familial prostate cancer and non-familial cancer (65.3 years versus 66.6 years).

The positive predictive value of a PSA value above $3.0 \mu\text{g l}^{-1}$ was higher in men with a family history of prostate cancer (28.6%), than among those without an affected first-degree relative (17.9%; $P = 0.005$). However, the increase in predictive value associated with a positive family history was restricted to the subgroup of men with a normal digital rectal examination (Table 2). These unexpected results are explainable by the high frequency of false-positive rectal examinations observed in men with a positive family history. Among men with a brother affected with prostate cancer, 13.0% had a false-positive rectal examination (i.e., specificity of 87.0%), compared with only 5.5% of men without a family history of prostate cancer (specificity of 94.5%) ($P < 0.001$). The mean PSA and mean log (PSA) values were also higher in healthy men with a positive family history, but these differences were not statistically significant. The cause of the false positive tests is unclear, but a proportion of these are likely to be cases of benign prostatic hyperplasia. In a previous study it was reported that a family history of prostate disease (cancer or hyperplasia) was more frequent in relatives of men with benign hyperplasia (20%) than in relatives of men with prostate cancer (12.8%) or healthy con-

trols (5.1%)⁷. These data suggest that common genetic mechanisms may predispose to benign and malignant prostate disease.

The results of our study indicate a greater prevalence of detectable prostate cancer among subjects who reported an affected brother than among the general population. The relative risk for those who reported an affected father was not found to be equally high. These data are consistent with a recessive, or X-linked, genetic component to prostate cancer inheritance. It is possible that the environment shared by brothers is more similar than that shared by fathers and sons. It is important to define accurately the genetic model of prostate cancer inheritance in order to provide genetic counselling to family members, and if genetic markers are to be employed in efforts to identify prostate cancer susceptibility genes.

Past studies have suggested that prostate cancer susceptibility is best modelled as a dominant trait. In a large case-control study 691 cases⁸, a relative risk of 3.0 was found for brothers of men with prostate cancer, 2.0 for fathers, 1.9 for grandfathers and 1.7 for uncles. A segregation analysis performed on this set of families led these investigators to conclude that prostate cancer inheritance best fitted an autosomal dominant model, where a rare susceptibility gene with a high lifetime penetrance was transmitted⁹. It is surprising that the odds ratio for a first-degree relative in the Steinberg study was 2.1 and was not significantly different from the odds ratio for a second-degree relative (1.8). For both dominant and recessive genetic diseases, the attenuation of relative risk between first- and second-degree relatives is expected to be greater than this. Furthermore, the frequency of prostate cancer was reported to

Table 2 Positive predictive value of a PSA > 3.0 µg l⁻¹ by results of rectal examination and by family history of prostate cancer

	PPV of PSA > 3.0 µg l ⁻¹ for prostate cancer	
	Normal rectal examination	Abnormal rectal examination
Negative family history	12.1% (117/964)	48.9% (87/178)
Positive family history	27.4% (26/95)	33.3% (8/24)

Because we found significant under-reporting of prostate cancer in second-degree relatives, only those with a father or brother affected are considered to have a positive family history in this table. Actual numbers of tests are presented in brackets.

be 7.5% in the fathers of controls but only 2.7% in uncles of controls. There is no plausible reason why the rate in uncles of controls should be less than that for fathers, and the potential for under-reporting, and recall bias, is high. Prostate cancer patients may be more likely to be aware of the diagnosis of prostate cancer in relatives, may be more diligent in their search for additional cases, or may be more likely to misinterpret benign disease as cancer, than healthy controls. The effect of this recall bias will be to increase the magnitude of the relative risks associated with a family history, especially for second-degree relatives, where the information is less certain. It is possible that the accuracy of the reporting of prostate cancer in brothers is better than for fathers because the diagnosis of prostate cancer in a brother is likely to be much more recent than the diagnosis in a father.

In our study, recall bias was unlikely to influence our results because the family history was obtained before the diagnosis of prostate cancer was made. In an early study Woolf used methods that were not sensitive to recall bias and obtained re-

sults similar to ours¹⁰. Deaths from prostate cancer among 228 cases and their relatives were identified by review of the Utah state vital statistics records. The observed numbers of deaths were compared with the expected number based on rates from the Utah State Bureau of Vital Statistics and with deaths in a control group. There were 12 deaths from prostate cancer among brothers of prostate cancer cases, compared with 4.3 expected (RR = 2.81; *P* = 0.002), and 3 deaths in fathers compared with 2.4 expected (RR = 1.25; not significant).

Family history is currently among the few variables that are used in practice to identify men at high risk for prostate cancer in North America. Some physicians now recommend that screening with PSA be actively encouraged for men with affected first-degree relatives. To our knowledge, ours is the first study to evaluate the impact of this recommendation. Our data emphasize the importance of recording the family history when evaluating a man for prostate cancer. The information may be used to identify men at high risk and to help in the interpretation of positive screening tests.

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