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Modifiable risk factors for prostate cancer mortality in London: forty years of follow-up in the Whitehall study

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Abstract

Background—The determinants of prostate cancer – aside from established but non-modifiable risk factors of increased age, black ethnicity and a positive family history – are poorly understood.

Methods—We examined the association of a series of baseline socioeconomic, behavioural and metabolic characteristics with the risk of prostate cancer mortality in a 40 year follow-up of the original Whitehall cohort study which gave rise to 578 prostate cancer deaths in 17,934 men.

Results—After adjustment for a series of baseline covariates, results from proportional hazards regression analyses indicated that marital status (hazard ratio; 95% confidence interval: widowed/divorced vs. married: 1.44; 0.95, 2.18), raised blood cholesterol (tertile 3 vs. 1: 1.35; 1.11, 1.65), and increased physical stature (tertile 3 vs. 1: 1.37; 1.09, 1.74) were associated with death from prostate cancer, although statistical significance at conventional levels was not apparent in all analyses. There was no evidence that physical activity, smoking habit, socio-economic status, either component of blood pressure, nor diabetes predicted the risk of death from this malignancy herein.

Conclusions—In the present study there was a suggestion that marital status, blood cholesterol and height were risk indices for death from prostate cancer.

Keywords

epidemiology; risk factors; prostate cancer

Introduction

Although carcinoma of the prostate is the most common malignancy in men in western societies,[1] its aetiology – beyond the established but non-modifiable risk indices of increased age, black ethnicity, and a positive family history[2] – is very poorly understood. The observation that men migrating from areas of low to high prostate cancer incidence adopt the disease rates of their new country within only one generation[3] strongly implicates a key role for environmental factors in the occurrence of this neoplasm.

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To date, and despite having *a priori* biological plausibility, results from population-based studies exploring behavioural risk factors for both fatal and non-fatal prostate cancer, such as physical inactivity[4;5] and smoking,[6] are highly inconsistent. Recently, investigators have also examined the capacity of the metabolic correlates of these behaviours such as blood pressure,[7] serum cholesterol,[8–10] obesity[2] and diabetes[11] to predict future prostate cancer. Again, findings from a modest series of cohort studies, many of which are underpowered, are discordant or suggest null associations.

Four decades of mortality surveillance of men in the original Whitehall study[12] have given rise to a large number of deaths ascribed to prostate cancer. This allows us address these issues of data paucity, suboptimal study size, and inconsistent results by examining the relation, if any, of a comprehensive range of socioeconomic, physiological, and behavioural risk factors with prostate cancer mortality.

Methods

In the Whitehall study, data were collected on 19,019 male, non-industrial, government employees aged from 40 to 69 years when examined between 1967 and 1970 in London (UK), representing a 77% response.[12] This involved the completion of a study questionnaire and participation in a medical examination, both of which have been described in detail elsewhere.[12] In brief, the questionnaire included enquiries regarding civil service employment grade (an indicator of socio-economic status[13]), smoking habits,[14] marital status,[15] and physical activity. During the course of baseline data collection, the physical activity questions were modified such that 12889 men responded to enquiries about travel activity[16] and 6954 were asked about their leisure activity.[17] For travel activity, cohort members indicated how many minutes they walked or bicycled to work each day (single journey). For leisure activity, study members were asked to specify their hobbies or sports; they were then classified as inactive, moderately active, or active during leisure.[24]

Blood pressure,[18] height,[19] weight,[20] pulmonary function (indexed by forced expiratory volume in one second, FEV1),[21] and, following an overnight fast, plasma cholesterol[22] and post-challenge blood glucose concentration,[23] were all determined using standard protocols.[12] Body mass index (BMI) was computed using the standard formulae (weight[kg]/height^2[m^2]).

In this study, a 10% representative subgroup of 1618 participants completed a three day (Saturday/Sunday and two week days) dietary record during the period of baseline examination.[24] The standard dietary records, listing unweighed but semi-quantitative descriptions of all food and drink consumed, were coded with use of a comprehensive food table. Data were extracted on dietary characteristics which, *a priori*, we had reason to anticipate an association with carcinoma of the prostate:[2] intake of alcohol, fat (including animal, dairy, saturated, monounsaturated, polyunsaturated), calcium, linoleic acid, dietary cholesterol, retinol, and beta-carotene.

A total of 18,880 men (99.3% of participants in baseline survey) were traced using the UK National Health Service Central Registry and prostate cancer deaths were ascertained from death certificates (coded as ICD 8/9: 185, ICD 10: C61). The present analyses are based on 17,934 men with complete data; the outcome of interest throughout our analyses was prostate cancer mortality.

The person years of follow-up for each man was partitioned by age at risk using 5-years age groups. To summarise the relationship between each risk factor and prostate cancer mortality we used Cox's proportional hazards regression model to produce hazard ratios (HRs) with accompanying 95% confidence intervals. Censoring was made for age at death,

age at loss to follow-up, or age at end of follow-up – whichever came first. These analyses were first adjusted for age at risk and then fully-adjusted for all potential confounding and mediating factors. Tests for trend across physical activity levels were computed by fitting a linear trend term.

Results

During a maximum of 40 years of follow-up there were 13,948 deaths from all-causes in the present analytical sample, 578 (4.2 %) of which were ascribed to prostate cancer. As expected, age was strongly related to death from carcinoma of the prostate: HR per 10 year increase; 95% confidence interval: 3.52; 3.21, 3.85). In table 1 we show the associations between prostate cancer and a series of baseline physiological characteristics. Although categories of body mass index were not associated with prostate mortality risk, there was a higher rate of mortality from this carcinoma apparent in men with elevated plasma cholesterol levels, an effect that was robust to statistical adjustment for a range of covariates. Neither component of blood pressure nor diabetes offered any predictive capacity for prostate cancer. Men with increased pulmonary function, as indexed by FEV1, and those who were taller, experienced a raised risk of prostate cancer. After mutual control, the impact of FEV1 was greatly reduced, while the effect for taller men held.

In table 2 we depict the association of behavioural and psychosocial risk factors with death from carcinoma of the prostate. There was no suggestion that smoking or either index of physical activity was associated with this malignancy. There was also no evidence of a relation between socioeconomic status and prostate cancer, however, there was an association with marital status such that being single at baseline conferred protection, while being widowed or divorced was associated with elevated risk compared to married men.

Finally, in the 1618 men with data on dietary characteristics there were 60 deaths from prostate cancer during follow-up (Table 3). There was no strong suggestion of an association between any of the selected dietary characteristics – alcohol, fat (including animal, dairy, saturated, monounsaturated, polyunsaturated), calcium, linoleic acid, dietary cholesterol and beta-carotene – and death from this malignancy.

Discussion

In this large prospective cohort study with almost complete follow-up of its members, of the eleven risk factors examined in relation to prostate cancer mortality, there was a suggestion that being widowed or divorced, higher levels of plasma cholesterol, and increased physical stature were associated with elevated risk. The magnitude of these relationships was generally modest and, although the associations of marital status, plasma cholesterol and physical stature were not attenuated with adjustment for the measured covariates, they could plausibly be explained by residual confounding by other unmeasured factors or, given the large number of exposure variables, the problem of multiple comparisons. There was essentially no association between the dietary variables and later prostate cancer mortality risk, although these analyses were hampered by a modest number of cases.

In keeping with our own results, studies examining the relationship between plasma or blood cholesterol and prostate cancer risk typically reveal positive associations,[25;26] although this is not a universal observation.[27–29] A series of reports suggest taller men are more likely to experience prostate cancer than their shorter counterparts.[30–32] Our observation in some analyses that elevated lung function confers some increased risk of prostate carcinoma has, to our knowledge, not been previously examined. Both lung function and stature may be conceptualised as markers of pre-adult exposures,[21] and, while under a degree of genetic

control, probably capture nutrition during this period.[33] It is plausible that over-feeding during selected periods across the life course stimulate carcinogenesis.[34] Underlying this relation may be levels of insulin-like growth factors (IGF) which correlate directly with caloric intake (in animals),[35] height in children,[36] and risk of prostate cancer in adult humans.[37] A separate explanation for the positive height–cancer effects evident in the present analysis simply posits that taller people have larger bodies and therefore more cells that may potentially undergo malignant transformation to cancer.[38]

This study has several strengths, including: its large sample size which leads to a greater number of fatal prostate cancer events than most other studies, prospective design, statistical control of a range of potential mediating and confounding variables, and almost complete follow-up for mortality. Weaknesses include: the absence of measurement of other potential risk factors such as hormone levels and exposure to environmental pesticides; some of the risk factor-prostate cancer mortality relationships we explored were not hypothesis-driven; examining the influence of multiple exposures on prostate cancer death may have led to positive results surfacing by chance alone; and, owing to a lack of data, we were unable to examine if the risk factors for prostate cancer mortality – our only endpoint of interest – differed to those for prostate cancer incidence. While misclassification of the exposures variables may have occurred, this is likely to be random with respect to the outcome of interest, so resulting in an underestimation of the magnitude of the effect estimates.

In conclusion, in the present study there was a suggestion that being widowed or divorced, and higher levels of plasma cholesterol, and physical stature were associated with higher rates of prostate cancer mortality.

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Table 1

Physiological risk factors for prostate cancer mortality in the original Whitehall Study (578 prostate cancer deaths among 17934 men)

Risk factor, units (mean [SD])		No. deaths / Person years (1000s)	Hazard ratio (95% confidence intervals)	
			Age-adjusted	Multiple-adjustment[a]
Body mass index, kg/m^2	Underweight (<18.5)	5 / 5.0	1.00 (0.41, 2.42)	1.00 (0.41, 2.44)
(24.75 [2.96])	Normal weight (18.5–24.9)	323 / 260.9	1.0 (ref)	1.0 (ref)
	Overweight (25.0–29.9)	233 / 189.1	1.03 (0.93, 1.15)	1.04 (0.93, 1.16)
	Obese (30+)	17 / 17.1	0.93 (0.57, 1.53)	1.00 (0.61, 1.65)
	Per 1 SD increase		1.02 (0.94, 1.12)	1.04 (0.94, 1.14)
	P-value for trend		0.74	0.91
Plasma cholesterol (mmol/l)	Tertile 1 (<4.54)	176 / 163.0	1.0	1.0
(5.10 [1.21])	Tertile 2 (4.54–5.54)	177 / 151.5	1.08 (0.88, 1.33)	1.07 (0.87, 1.32)
	Tertile 3 (>5.54)	225 / 157.8	1.36 (1.12, 1.66)	1.35 (1.11, 1.65)
	Per 1 SD increase		1.12 (1.04, 1.22)	1.12 (1.03, 1.22)
	P-value for trend		0.002	0.003
Diastolic blood pressure (mmHg)	Tertile 1 (<78)	206 / 159.2	1.0	1.0
(84.5 [13.8])	Tertile 2 (78–88)	200 / 168.8	0.94 (0.77, 1.14)	0.91 (0.75, 1.11)
	Tertile 3 (>88)	172 / 144.2	1.00 (0.82, 1.22)	0.98 (0.79, 1.21)
	Per 1 SD increase		1.00 (0.91, 1.09)	0.99 (0.90, 1.08)
	P-value for trend		0.96	0.82
Systolic blood pressure (mmHg)	Tertile 1 (<126)	217 / 169.3	1.0	1.0
(136.4 [21.2])	Tertile 2 (126–142)	200 / 165.3	0.94 (0.78, 1.14)	0.94 (0.77, 1.13)
	Tertile 3 (>142)	161 / 137.6	0.92 (0.75, 1.13)	0.93 (0.75, 1.15)
	Per 1 SD increase		0.96 (0.88, 1.05)	0.96 (0.88, 1.06)
	P-value for trend		0.40	0.47
Diabetes[b]	Normoglycaemia	548 / 445.1	1.0	1.0
(4.17 [0.71])	IGT	29 / 22.7	1.11 (0.76, 1.61)	1.16 (0.80, 1.70)
	Diabetes	1 / 4.4	0.22 (0.03, 1.56)	0.24 (0.03, 1.73)
	P-value for trend		0.50	0.72
Lung function (FEV1, L)	Tertile 1 (<2.9)	131 / 117.8	1.0	1.0
(3.14 [0.72])	Tertile 2 (2.9–3.4)	232 / 161.4	1.36 (1.10, 1.68)	1.25 (1.00, 1.56)
	Tertile 3 (>3.4)	215 / 193.0	1.18 (0.95, 1.47)	1.02 (0.80, 1.31)
	Per 1 SD increase		1.08 (0.99, 1.18)	1.01 (0.91, 1.12)
	P-value for trend		0.23	0.89
Height (m)	Tertile 1 (<1.73)	133 / 123.0	1.0	1.0
(1.758 [0.068])	Tertile 2 (1.73–1.78)	215 / 179.1	1.19 (0.96, 1.48)	1.19 (0.95, 1.48)
	Tertile 3 (>1.78)	230 / 170.1	1.39 (1.12, 1.72)	1.37 (1.09, 1.74)
	Per 1 SD increase		1.12 (1.03, 1.22)	1.11 (1.01, 1.22)
	P-value for trend		0.002	0.008

[a] multiple adjustment is adjustment for BMI, plasma cholesterol, physical activity, socio-economic status, diabetes/blood glucose, marital status, FEV1, height, age at risk, smoking, and diastolic and systolic blood pressure (estimates for components of blood pressure are not mutually adjusted).

[b] diabetes was defined as blood glucose of ≥11.1 mmol/l (≥200 mg/100ml) and/or a positive response to the questionnaire enquiry “are you, or have you been, diabetic?”; and impaired glucose tolerance (IGT) as 5.4 to 11.0 mmol/l (96 to 199 mg/100ml). All other men were denoted normoglycaemic. The Mean (SD) blood glucose reported here is for the 17699 men who were classified as either normoglycaemic or as having IGT.

Table 2

Behavioural and psychosocial risk factors for prostate cancer mortality in the original Whitehall Study (578 prostate cancer deaths among 17934 men)

Risk factor, units		Percent	No. deaths / Person years (1000s)	Hazard ratio (95% confidence intervals)	
				Age-adjusted	Multiple-adjustment*
Leisure activity	None / inactive	35.6	55 / 57.0	1.0 (ref)	1.0 (ref)
	Moderately active	41.1	96 / 71.5	1.30 (0.93, 1.81)	1.24 (0.88, 1.73)
	Active	23.3	53 / 43.3	1.19 (0.81, 1.73)	1.12 (0.76, 1.64)
	P-value for trend			0.35	0.56
Travel activity (mins./day)	0 – 9	19.6	63 / 61.5	1.0	1.0
	10 – 19	44.8	182 / 144.1	1.23 (0.92, 1.64)	1.24 (0.93, 1.66)
	20 – 29	25.3	108 / 83.7	1.23 (0.90, 1.67)	1.26 (0.92, 1.72)
	30 – 39	8.3	36 / 27.0	1.28 (0.85, 1.92)	1.30 (0.86, 1.97)
	40+	2.0	11 / 6.2	1.60 (0.84, 3.03)	1.65 (0.87, 3.15)
	P-value for trend			0.14	0.10
Socio-economic position	Administrative (highest)	5.1	35 / 27.3	0.98 (0.70, 1.39)	0.93 (0.65, 1.31)
	Professional/executive	65.1	401 / 325.8	1.0	1.0
	Clerical	15.8	73 / 62.9	0.90 (0.70, 1.16)	0.96 (0.74, 1.25)
	Other	9.4	35 / 32.7	0.78 (0.55, 1.10)	0.83 (0.58, 1.19)
	BC & DS‡	4.7	34 / 23.5	1.20 (0.84, 1.69)	1.14 (0.80, 1.62)
	P-value for trend+			0.15	0.50
Marital status	Married	88.1	527 / 420.0	1.0	1.0
	Single	8.5	27 / 38.9	0.67 (0.45, 0.98)	0.70 (0.47, 1.03)
	Widowed / divorced	3.4	24 / 13.3	1.37 (0.91, 2.06)	1.44 (0.95, 2.18)
	P-value for heterogeneity			0.03	0.03
Smoking habit	Never smoked	18.3	123 / 99.5	1.0	1.0
	Ex-smoker	36.6	225 / 179.8	0.95 (0.76, 1.18)	0.94 (0.76, 1.18)
	Pipe / cigar smoker	3.5	27 / 17.0	1.23 (0.81, 1.87)	1.24 (0.82, 1.88)
	Current cigarette smoker	41.6	203 / 175.8	1.10 (0.88, 1.37)	1.14 (0.91, 1.44)
	P-value for trend			0.20	0.09

[‡] British Council & Diplomatic Service are included as a separate category as they are not directly comparable with other civil service departments.

[+] British Council & Diplomatic Service are excluded from test for trend.

[*] multiple adjustment is adjustment for BMI, plasma cholesterol, physical activity, socio-economic status, diabetes/blood glucose, marital status, FEV1, height, age at risk, smoking, and diastolic and systolic blood pressure (estimates for components of blood pressure are not mutually adjusted).

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Table 3

Dietary risk factors for prostate cancer mortality in the original Whitehall Study (60 prostate cancer deaths among 1618 men)

Risk factor, units (mean [SD])		No. deaths / Person years (1000s)	Hazard ratio (95% confidence intervals)	
			Age-adjusted	Multiple-adjustment[a]
Alcohol, g/day	None	17 / 13.7	1.0 (ref)	1.0 (ref)
(14.3 [22.2])	1 – 9	22 / 12.3	1.31 (0.70, 2.47)	1.55 (0.81, 3.00)
	10 – 34	14 / 11.6	0.80 (0.39, 1.59)	0.96 (0.46, 1.98)
	35+	7 / 5.4	1.11 (0.46, 2.67)	1.52 (0.60, 3.85)
	P-value for trend	-	0.70	0.74
Fat, g	Tertile 1 (<98.3)	25 / 13.6	1.0	1.0
(110.5 [29.2])	Tertile 2 (98.3–120.8)	19 / 14.5	0.73 (0.40, 1.33)	0.77 (0.42, 1.42)
	Tertile 3 (>120.8)	16 / 14.9	0.58 (0.31, 1.08)	0.57 (0.30, 1.09)
	Per 1 SD increase	-	0.87 (0.66, 1.15)	0.85 (0.64, 1.13)
	P-value for trend	-	0.08	0.09
Animal fat, g	Tertile 1 (<30.7)	27 / 13.8	1.0	1.0
(38.4 [15.7])	Tertile 2 (30.7–43.6)	16 / 14.5	0.51 (0.28, 0.95)	0.49 (0.26, 0.94)
	Tertile 3 (>43.6)	17 / 14.7	0.61 (0.33, 1.12)	0.53 (0.28, 1.01)
	Per 1 SD increase	-	0.85 (0.65, 1.11)	0.79 (0.60, 1.05)
	P-value for trend	-	0.09	0.05
Dairy fat, g	Tertile 1 (<42.3)	19 / 14.2	1.0	1.0
(50.9 [18.4])	Tertile 2 (42.3–56.7)	24 / 14.2	1.34 (0.73, 2.45)	1.40 (0.76, 2.57)
	Tertile 3 (>56.7)	17 / 14.6	0.88 (0.46, 1.70)	0.94 (0.48, 1.85)
	Per 1 SD increase	-	0.92 (0.71, 1.19)	0.94 (0.72, 1.22)
	P-value for trend	-	0.72	0.91
Saturated fat, g	Tertile 1 (<50.5)	20 / 13.7	1.0	1.0
(56.9 [15.0])	Tertile 2 (50.5–62.1)	25 / 14.4	1.20 (0.67, 2.16)	1.30 (0.72, 2.35)
	Tertile 3 (>62.1)	15 / 14.9	0.68 (0.35, 1.33)	0.68 (0.34, 1.35)
	Per 1 SD increase	-	0.86 (0.66, 1.13)	0.85 (0.65, 1.12)
	P-value for trend	-	0.27	0.30
Monounsaturated fat, g	Tertile 1 (<40.0)	25 / 13.6	1.0	1.0
(45.4 [12.3])	Tertile 2 (40.0–49.7)	17 / 14.6	0.63 (0.34, 1.16)	0.65 (0.35, 1.22)
	Tertile 3 (>49.7)	18 / 14.8	0.66 (0.36, 1.21)	0.64 (0.34, 1.21)
	Per 1 SD increase	-	0.87 (0.66, 1.15)	0.85 (0.64, 1.13)
	P-value for trend	-	0.16	0.15
Polyunsaturated fat, g	Tertile 1 (<6.8)	24 / 13.7	1.0	1.0
(7.9 [2.8])	Tertile 2 (6.8–8.7)	18 / 14.9	0.72 (0.39, 1.33)	0.74 (0.39, 1.37)
	Tertile 3 (>8.7)	18 / 14.4	0.81 (0.44, 1.49)	0.81 (0.43, 1.52)
	Per 1 SD increase	-	0.90 (0.68, 1.20)	0.89 (0.67, 1.20)
	P-value for trend	-	0.46	0.48
Calcium, mg	Tertile 1 (<983)	17 / 13.7	1.0	1.0

Risk factor, units (mean [SD])		No. deaths / Person years (1000s)	Hazard ratio (95% confidence intervals)	
			Age-adjusted	Multiple-adjustment[a]
(1140 [321])	Tertile 2 (983–1255)	25 / 14.9	1.19 (0.64, 2.20)	1.24 (0.66, 2.31)
	Tertile 3 (>1255)	18 / 14.4	0.96 (0.50, 1.87)	0.90 (0.46, 1.77)
	Per 1 SD increase	-	1.07 (0.83, 1.38)	1.01 (0.78, 1.31)
	P-value for trend	-	0.90	0.75
Linoleic acid, g	Tertile 1 (<4.86)	22 / 13.7	1.0	1.0
(5.75 [2.19])	Tertile 2 (4.86–6.27)	18 / 14.6	0.78 (0.42, 1.45)	0.80 (0.43, 1.50)
	Tertile 3 (>6.27)	20 / 14.6	0.87 (0.48, 1.60)	0.84 (0.45, 1.56)
	Per 1 SD increase	-	0.93 (0.70, 1.24)	0.91 (0.68, 1.22)
	P-value for trend	-	0.66	0.57
Cholesterol, g	Tertile 1 (<449)	25 / 14.4	1.0	1.0
(558 [212])	Tertile 2 (449–631.8)	17 / 14.1	0.72 (0.39, 1.34)	0.75 (0.40, 1.40)
	Tertile 3 (>631.8)	18 / 14.5	0.74 (0.40, 1.36)	0.75 (0.40, 1.38)
	Per 1 SD increase	-	0.81 (0.62, 1.07)	0.82 (0.62, 1.09)
	P-value for trend	-	0.32	0.34
Retinol, µg	Tertile 1 (<565)	25 / 13.6	1.0	1.0
(1432 [2041])	Tertile 2 (565–867)	16 / 14.4	0.55 (0.29, 1.02)	0.57 (0.30, 1.08)
	Tertile 3 (>867)	19 / 15.0	0.61 (0.34, 1.11)	0.57 (0.31, 1.04)
	Per 1 SD increase	-	0.74 (0.55, 0.99)	0.72 (0.54, 0.97)
	P-value for trend	-	0.10	0.07
Beta-carotene, µg	Tertile 1 (<1082)	13 / 13.5	1.0	1.0
(2634 [2665])	Tertile 2 (1082–2403)	23 / 14.6	1.50 (0.76, 2.96)	1.61 (0.81, 3.19)
	Tertile 3 (>2403)	24 / 14.9	1.42 (0.72, 2.78)	1.33 (0.67, 2.64)
	Per 1 SD increase	-	1.08 (0.84, 1.39)	1.01 (0.79, 1.30)
	P-value for trend	-	0.36	0.50

[a] multiple adjustment is adjustment for BMI, plasma cholesterol, physical activity, socio-economic status, diabetes/blood glucose, marital status, FEV1, height, age at risk, smoking, and diastolic and systolic blood pressure (estimates for components of blood pressure are not mutually adjusted).