EUROPEAN JOURNAL OF CANCER 43 (2007) 1060–1065

available at www.sciencedirect.com

journal homepage: www.ejconline.com

The role of self-reported stress in the development of breast cancer and prostate cancer: A prospective cohort study of employed males and females with 30 years of follow-up

Chris Metcalfe[a,*], *George Davey Smith*[a], *John Macleod*[b], *Carole Hart*[c]

[a]*Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, United Kingdom*
[b]*Department of Primary Care and General Practice, University of Birmingham, Birmingham, United Kingdom*
[c]*Public Health and Health Policy, Division of Community Based Sciences, University of Glasgow, Glasgow, United Kingdom*

ARTICLE INFO

Article history:
Received 17 October 2006
Received in revised form 13 December 2006
Accepted 4 January 2007
Available online 1 March 2007

Keywords:
Breast neoplasms
Mortality
Prospective studies
Prostatic neoplasms
Scotland
Socioeconomic factors
Stress, psychological

ABSTRACT

We investigate the association between psychological stress and breast cancer and, as oestrogen may provide a common mechanism, the association between stress and prostate cancer. A prospective study of 991 women and 5743 men employed in Scotland in the 1970s provided data. Risk exposure was measured by questionnaire and physical examination, routine data collection provided cancer outcomes over the subsequent 30 years. There was weak evidence of elevated incidences in those reporting moderate (breast cancer: hazard ratio [HR] 2.16, 95% CI 1.00–4.71; prostate cancer: HR 1.65, 95% CI 1.20–2.27) and high stress (breast cancer: HR 1.92, 95% CI 0.81–4.55; prostate cancer: HR 1.35, 95% CI 0.87–2.10) compared to those reporting low stress. These estimates are adjusted for socioeconomic circumstances and health-related behaviours. With no dose–response relationship and no established mechanism linking stress with breast and prostate cancer, confounding is the parsimonious explanation of these findings.

1. Introduction

A number of recent prospective studies have provided evidence that relatively high levels of psychological stress are associated with the subsequent diagnosis of breast cancer in women. A lower incidence of breast cancer has been linked with psychological stress[1] and, in the Nurses' Health Study, high job demands.[2] In contrast, a higher incidence of breast cancer has been linked with greater psychological stress[3] and, in the Finnish Twin Cohort,[4] stressful life events. Oestrogen secretion has been suggested as a mechanism by which stress can affect the risk of breast cancer, with chronic psychological stress suppressing[1] or amplifying[2] oestrogen secretion according to these hypotheses.

In this context of conflicting results and hypotheses, it is not surprising that not all recent studies find evidence of an association. Notably there was no association between caregiving stress and breast cancer in the Nurses' Health Study,[5] nor between stress of daily activities and breast cancer in the Finnish Twin Cohort,[6] both of these studies having been cited above in support of an association. In addition, two recent meta-analyses on the association between stressful life

* *Corresponding author:* Tel.: +44 (0) 117 928 7326; fax: +44 (0) 117 928 7325.
E-mail address: chris.metcalfe@bristol.ac.uk (C. Metcalfe).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.01.027

events and breast cancer have failed to find convincing evidence of an association once study quality and publication bias have been accounted for.[7,8] Earlier studies have been criticised for using retrospective or cross-sectional designs,[9,10] which leave reported psychological stress prone to recall bias, and for failing to control all relevant confounding factors.[9] With regards to the latter issue, it has been reported that women reporting high levels of psychological stress are more likely to be less physically active, to have finished full-time education earlier, to have a manual occupation, to be heavy drinkers, to be a current smoker, and to have undergone hormone therapy.[1,6]

We have previously suggested that confounding by factors associated with social position may have been underestimated when inferring causality from associations between measures of psychological distress and chronic physical disease. Social position often varies with both reported distress and health outcomes, so potentially confounding observed associations between these two factors. Hence in a population where social advantage is associated with perceived stress and social disadvantage with lung cancer, higher stress appears associated with lower risk of lung cancer despite an association between higher stress and heavier smoking.[11] Conversely, in a population where social disadvantage is associated with perceived stress and social advantage is associated with breast cancer, higher stress appears associated with a lower risk of breast cancer.[1,11,12]

This study is based upon a cohort of women for whom reported stress is not strongly associated with social position,[13] limiting the extent to which social position can confound the observed association between psychological stress and breast cancer. Furthermore, extensive data are available on social position and other potentially confounding factors, allowing better control than in many previous studies. We also look at the association between reported daily stress and prostate cancer in men. If psychological stress is affecting the rate of breast cancer through a hormonal mechanism, a similar mechanism may also influence hormone-dependent cancer in males.[14]

2. Materials and methods

2.1. Participants

The data for this analysis come from the West of Scotland Collaborative Study.[15,16] In brief, a cohort of 6022 men and 1006 women were recruited from a variety of workplaces in the west of Scotland between 1970 and 1973. At enrollment, all members of the cohort were invited to complete a questionnaire and undergo a physical examination. The present analysis is based upon 5743 men and 991 women, aged 35–64 years old at recruitment, who provided full data on the variables used. Only 11 individuals were lost to follow-up.

2.2. Outcome variables

Each cohort member was followed up through linkage to the National Health Service (NHS) Central Register until they left the United Kingdom, until they died, or otherwise until 31st March 2004. Breast cancer events (deaths, cancer registrations and hospital discharge diagnoses) were detected as International Classification of Diseases 9th revision (ICD-9) code 174 or ICD-10 code C50, whereas prostate cancer events were detected as ICD-9 code 185 or ICD-10 code C61. Death due to breast cancer, and first recorded instance of breast cancer were used as outcome measures for women. Death due to prostate cancer, and first recorded instance of prostate cancer were used as outcome measures for men. The small number of breast cancers occurring in men were not included in the analysis.

2.3. Risk factors and confounding variables

Psychological stress was measured at enrollment using the Reeder Stress Inventory,[17] a self-report measure of daily stress we have described in detail elsewhere.[18] Respondents are asked whether each of the four statements describes them ‘exactly’, ‘to some extent’, ‘not very accurately’, or ‘not at all’. The four statements are ‘In general I am usually tense or nervous’, ‘There is a great amount of nervous strain connected with my daily activities’, ‘At the end of the day I am completely exhausted mentally and physically’, and ‘My daily activities are extremely trying and stressful’. Scores range from 1 (low stress) to 8 (high stress), with three categories of stress being used in the presentation of the results: low stress (scores 1–3), medium stress (scores 4 and 5) and high stress (scores 6 and 7). Despite its age, the factor structure,[13] construct validity and test–retest reliability of the Reeder Stress Inventory support its continued use.[18]

Measures of social position in adulthood and childhood were available. Social position in adulthood was captured through the individual’s reported occupation at enrollment (manual versus non-manual according to the Registrar General’s classification[19]), their age at leaving full-time education (up to 14 years versus 15 years or older) and the Carstairs and Morris Index for their usual area of residence (categorised as affluent scores 1–3, intermediate scores 4 and 5, deprived scores 6 and 7[20]). An individual’s social circumstances in childhood were ascertained from their father’s main occupation (manual versus non-manual), how many siblings they had (0–2, 3–4, 5–6 and 7 or more siblings), and their height.

Height and weight were recorded using standard methods.[15,16] Exercise outside work was reported in hours per week and was categorised as less than 5 h, 5 h or more but less than 10 h, and 10 h or more, for men and women. Each participant’s average consumption of alcohol per week was derived from reported consumption of wine, beer and spirits.[21] For women three categories of alcohol consumption were derived, these being zero units, one to seven units, and eight or more units per week where one UK unit is 10 g of alcohol. For men six categories were derived, these being 0 units, 1–7 units, 8–14 units, 15–21 units, 22–34 units, and 35 or more units. The following aspects of each individual’s reported cigarette smoking history were used in the current analysis: number of cigarettes smoked per day if a current smoker (categorised as 1–14, 15–24, and 25 or more), whether an ex-smoker if not currently smoking, age at starting smoking, and whether or not the individual inhaled whilst smoking. Current cigarette smokers included those who reported having given up less than a year previously.[15,16] Only cigarette

smoking was considered here, with participants smoking cigars or a pipe only not being identified as smokers.

2.4. Statistical analysis

Proportional hazards models were used to estimate the associations between reported psychological stress and cancer outcomes. Age was the time scale in all models, with time at risk taken to start at the date of enrollment. In this way all analyses are age-adjusted. Reported stress, social position measures for adulthood, measures of social circumstances in childhood and other risk factors were added sequentially to models. For the fully adjusted effects of reported stress, the proportional hazards assumption was verified using a test based upon Schoenfeld residuals.[22] All analyses were undertaken using Stata 9 statistical software (StataCorp, College Station, TX, 2005).

3. Results

Over the 30 years of follow-up 17 of the 991 women died of breast cancer, and a further 45 were diagnosed with the disease. Of the 5743 men, 83 died of, and a further 161 were diagnosed with prostate cancer. In Table 1 the associations between the different measures of social position, the two types of cancer, and psychological stress are investigated. There is strong evidence of a higher incidence of breast cancer in taller women, and weak evidence of a higher incidence of prostate cancer in men who left full-time education aged 15 years or older, but otherwise the evidence of associations between social circumstances and breast or prostate cancer is limited. There is modest evidence that women raised in more affluent social circumstances, as measured by a taller adult height and a household shared with fewer siblings, report greater psychological stress in adulthood. For men, there is strong evidence of an association between all measures of more affluent social circumstances, in childhood and adulthood, and higher levels of reported stress.

In Table 2, the associations between reported psychological stress and the composite outcome of a subsequent diagnosis of, registration for, or death due to cancer are investigated. There is very weak evidence that women reporting medium or high levels of psychological stress at enrollment are more likely to develop breast cancer in the

Table 1 – Social position and mean (SD = standard deviation) reported psychological stress at enrollment, and cancer death, registration or hospital discharge diagnosis over the subsequent 30 years

	Women (n = 991)		Men (n = 5743)	
	Breast cancer (%)	Mean stress (SD)	Prostate cancer (%)	Mean stress (SD)
Own current occupation				
Manual	43 (5.6)	4.17 (1.68)	107 (3.8)	3.48 (1.75)
Non-manual	19 (8.6)	4.10 (1.57)	137 (4.7)	4.13 (1.49)
p-Value[a]	0.13	0.58	0.61	<0.001
Usual area of residence				
Deprived (scores 6 and 7)	26 (5.4)	4.20 (1.62)	57 (3.5)	3.62 (1.72)
Intermediate (scores 4 and 5)	30 (8.1)	4.13 (1.68)	101 (4.8)	3.73 (1.69)
Affluent (scores 1–3)	6 (4.3)	4.06 (1.72)	86 (4.3)	4.05 (1.54)
p-Value for trend[a]	0.92	0.30	0.55	<0.001
Left full-time education				
14 years old or younger	46 (6.3)	4.17 (1.67)	110 (3.8)	3.55 (1.73)
15 years old or older	16 (6.2)	4.11 (1.60)	134 (4.8)	4.07 (1.53)
p-Value[a]	0.85	0.82	0.058	<0.001
Father's main occupation				
Manual	57 (6.3)	4.14 (1.67)	181 (4.1)	3.70 (1.68)
Non-manual	5 (5.7)	4.35 (1.52)	63 (4.6)	4.15 (1.53)
p-Value[a]	0.77	0.30	0.59	<0.001
Height[b]				
Quartile 1 (Shortest)	16 (5.1)	3.98 (1.72)	64 (3.9)	3.64 (1.75)
Quartile 2	17 (5.4)	4.19 (1.62)	65 (4.0)	3.83 (1.62)
Quartile 3	12 (9.2)	4.37 (1.59)	59 (4.4)	3.85 (1.63)
Quartile 4 (Tallest)	17 (7.4)	4.22 (1.64)	56 (5.0)	3.97 (1.58)
p-Value for continuous measure[a]	0.005	0.059	0.26	<0.001
Number of siblings				
7+	17 (8.0)	4.00 (1.72)	34 (4.3)	3.46 (1.74)
5–6	14 (6.8)	4.11 (1.59)	37 (4.1)	3.59 (1.69)
3–4	15 (5.3)	4.11 (1.75)	71 (4.6)	3.80 (1.68)
0–2	16 (5.6)	4.35 (1.54)	102 (4.1)	4.00 (1.57)
p-Value for trend[a]	0.29	0.019	0.83	<0.001

a Age adjusted test.
b Quartiles for women are 139–155, 157–160, 162, 165–183 cm, and for men are 129–168, 170–173, 175–178, 180–196 cm.

Table 2 – Reported psychological stress and cancer death, registration or hospital discharge diagnosis over the subsequent 30 years. Each adjustment is in addition to those on the left

	Cancers/participants	Age-adjusted		+Adulthood socio-economic group[a] adjusted		+Childhood socioeconomic group[b] adjusted		+Risk factor[c] adjusted	
		Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Breast cancer (991 women)									
Low stress	8/248	1.00		1.00		1.00		1.00	
Medium stress	38/495	2.41	1.12–5.16	2.41	1.12–5.16	2.39	1.11–5.16	2.16	1.00–4.71
High stress	16/248	1.98	0.85–4.63	2.03	0.87–4.74	2.05	0.87–4.81	1.92	0.81–4.55
p for trend			0.15		0.15		0.15		0.24
Prostate cancer (5743 men)									
Low stress	53/1857	1.00		1.00		1.00		1.00	
Medium stress	158/3115	1.68	1.23–2.29	1.65	1.21–2.27	1.66	1.21–2.28	1.65	1.20–2.27
High stress	33/771	1.37	0.89–2.12	1.35	0.87–2.09	1.36	0.88–2.11	1.35	0.87–2.10
p for trend			0.010		0.016		0.013		0.017

a Current occupation, age when finishing full-time-education, Carstairs area deprivation index.
b Father's main occupation, height, number of siblings.
c Body mass index, exercise outside of work, alcohol consumption, and smoking history.

subsequent 30 years compared to women reporting lower levels of stress. The strongest evidence is for a difference between women reporting medium and low levels of psychological stress, with there being no evidence of particularly high rates of breast cancer in those women who had reported the highest levels of stress. The observed age-adjusted associations between psychological stress and subsequent breast cancer were not attenuated with additional control for measures of social position in childhood or adulthood. Further adjustment for risk factors did lead to a modest attenuation of the associations.

A similar picture is observed for associations between psychological stress and prostate cancer in men (Table 2). Men reporting medium or high levels of psychological stress at enrollment are more likely to develop prostate cancer compared to men reporting low levels of stress. Again, the strongest evidence is for a difference between men reporting medium compared to low levels of psychological stress, with there being no evidence of higher rates of prostate cancer in those men reporting the highest levels of stress. The age-adjusted associations between psychological stress and prostate cancer were not attenuated with additional control for measures of social position or risk factors. This same pattern of results was observed when only deaths due to prostate cancer were included in the outcome measure (data not shown).

4. Discussion

This prospective cohort study with 30 years of follow-up provides weak evidence to suggest that middle-aged women reporting medium or high levels of daily stress are at higher risk of developing breast cancer compared to those women reporting low levels of stress. A very similar association between medium or high levels of daily stress and the subsequent development of prostate cancer is seen in men. Neither breast cancer nor prostate cancer diagnoses were strongly socially patterned in this cohort. Though reported stress was higher in men in more affluent social circumstances, stress showed no strong association with social position in women. Moreover, age-adjusted associations between stress and cancer were not attenuated following further adjustment for measures of social position. Despite the limitations of statistical adjustment in the situation where confounders are measured imprecisely, these results together suggest that confounding by factors associated with social position is an unlikely explanation for the associations between stress and cancer risk observed.

We have previously reported that men and women reporting higher psychological stress in this cohort are more likely to have a lower body mass index (BMI), to smoke more cigarettes, to consume more alcohol and, for men, to undertake less recreational exercise.[13] Whereas age-adjusted associations between psychological stress and physiological measures were abolished by adjustment for social position, these associations between stress and measures of behaviour remain apparent once confounding by social position is controlled.[13] Despite this, the associations observed in the present analysis, between psychological stress, breast cancer and prostate cancer, were at most modestly attenu-

ated by additional adjustment for the effects of BMI, exercise outside of work, alcohol consumption and smoking. In particular, high alcohol consumption has been identified as increasing the risk of breast cancer,[23,24] but the lack of attenuation of the effect of psychological stress following adjustment for alcohol consumption suggests that the observed effect of psychological stress on breast cancer in the present study is not due to stress-induced increases in alcohol consumption.

Taller women have been identified as being at higher risk of breast cancer,[25,26] with this association being apparent in the present study. Taller women also reported higher levels of psychological stress but despite this there was no attenuation of the effect of stress on the incidence of breast cancer following adjustment for height. This is possibly due to height not so much allowing confounding by childhood social circumstances to be controlled, but instead reflecting a separate nutritional aetiology for breast cancer such as high childhood levels of insulin-like growth factor (IGF-I).[26] However, despite high levels of IGF-I being a recognised risk factor for prostate cancer,[14,27] there was no strong association between height and the incidence of prostate cancer in the present cohort. A number of other established risk factors for breast cancer were not measured in the present study, these being age at menarche, parity, and the age at which a woman had her first child.[24] Again, these factors may reflect a woman's socioeconomic position and so confound the psychological stress – breast cancer association, although this seems unlikely given the lack of an effect of adjusting for measured socioeconomic factors.

Oestrogen levels were not measured in this study, and so only indirect evidence is provided to address the hypothesised role for stress modulation of oestrogen levels in the aetiology of breast and prostate cancers. The association between high psychological stress and the increased rate of breast cancer observed in the present study is consistent with chronic psychological stress causing an increase in circulating oestrogen.[2] At first glance, the association between high psychological stress and an increased rate of prostate cancer suggests that psychological stress cannot also be increasing oestrogen in men. However, the available evidence from other epidemiological studies does not establish a protective effect of oestrogen, at physiological levels, for prostate cancer,[14] and in fact higher levels of oestrogen may interact with IGF-I synthesis to increase the risk.[14] The hypothesised effect of chronic psychological stress on oestrogen levels in women is challenged by results from the Nurses Health Study, where only weak associations were found between a greater number of hours spent in informal care giving and increased levels of estradiol and bioavailable estradiol.[5]

Few risk factors have been identified for prostate cancer, potentially due to most prostate cancers never becoming clinically apparent and the invasive nature of the tests required to identify pre-clinical disease. However, the available evidence suggests that cigarette smoking, alcohol and physical activity are not risk factors for prostate cancer,[27] and this is consistent with the findings of the present study, adjustment for these risk factors not attenuating the effect of psychological stress upon prostate cancer. Intuitively testosterone rather than oestrogen would be the hormone most likely involved in the aetiology of prostate cancer, but again the evidence from cohort studies is far from conclusive.[14,27] There is some evidence of chronic psychological stress suppressing testosterone levels[28,29], suggesting that stress could lower a man's risk of prostate cancer. However, evidence of an association has not been presented previously, and is not supported by the association of stress with a higher risk of prostate cancer in the present study.

Women were in the minority in the present cohort, with the consequent small number of events limiting the power of this study to investigate the association between psychological stress and breast cancer. Furthermore, almost all the women were employed at just two workplaces, and consequently the professional and managerial groups were poorly represented amongst the women. Further limitations to this study mentioned above were the lack of hormone, IGF-I and childbearing history measurements, and the reliance upon routine records for the identification of breast cancer and prostate cancer cases. A man can have prostate cancer for a number of years before it becomes clinically apparent, so risk factors identified in this study may be associated with cancer detection or progression rather than cancer aetiology.

In conclusion, this large prospective study with thirty years of follow-up has provided weak evidence of associations between high levels of self-reported psychological stress and subsequently increased rates of breast cancer and prostate cancer. While the potential for socioeconomic confounding of these results has been limited, other factors suggest that these observed associations alone are not convincing evidence of chronic psychological stress causing breast cancer or prostate cancer. Firstly, there was no simple 'dose–response' relationship. Cancer rates did not differ between individuals reporting moderate or high levels of psychological stress, only between these two groups and individuals reporting low levels of psychological stress. Secondly, while an association between chronic psychological stress and breast cancer has been proposed and investigated a number of times previously, the association between chronic psychological stress and prostate cancer has not. Indeed, the associations between psychological stress, breast cancer and prostate cancer are so similar that unless a common mechanism linking psychological stress and the two cancers can be proposed, the present results could be taken as evidence of a lack of specificity for the psychological stress and breast cancer association. Thirdly, there is no established biologically plausible mechanism by which psychological stress increases rates of breast and prostate cancer. Evidence from the present study cannot be used to address the hypothesised role of oestrogen until at least the role of oestrogen in prostate cancer aetiology is better established. With our present state of knowledge, confounding by a third unknown factor would appear to be the most parsimonious explanation behind the observed associations between psychological stress and the development of breast cancer and prostate cancer.

Conflict of interest statement

None declared.

Acknowledgements

The work of Victor Hawthorne, Charles Gillis, David Hole and Pauline MacKinnon has provided us with the data required for this analysis. A grant within phase two of the *Economic and Social Research Council's, Health Variations* research programme allowed linkage to hospital admission data. Permission to use the hospital admission data was given by the Privacy Advisory Committee. J.M. is supported by a Career Scientist fellowship from the Department of Health. All views expressed are those of the authors and not necessarily of the Department of Health.

REFERENCES

1. Nielsen NR, Zhang ZF, Kristensen TS, Netterstrom B, Schnohr M, Gronbaek M. Self reported stress and risk of breast cancer: prospective cohort study. *BMJ* 2005;**331**:548–50.
2. Schernhammer ES, Hankinson SE, Rosner B, et al. Job stress and breast cancer risk: the nurses' health study. *Am J Epidemiol* 2004;**160**:1079–86.
3. Helgesson O, Cabrera C, Lapidus L, Bengtsson C, Lissner L. Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women. *Eur J Cancer Prev* 2003;**12**:377–81.
4. Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M. Stressful life events and risk of breast cancer in 10,808 women: a cohort study. *Am J Epidemiol* 2003;**157**:415–23.
5. Kroenke CH, Hankinson SE, Schernhammer ES, Colditz GA, Kawachi I, Holmes MD. Caregiving stress, endogenous sex steroid hormone levels, and breast cancer incidence. *Am J Epidemiol* 2004;**159**:1019–27.
6. Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M. Stress of daily activities and risk of breast cancer: a prospective cohort study in Finland. *Int J Cancer* 2001;**91**:888–93.
7. Duijts SF, Zeegers MP, Borne BV. The association between stressful life events and breast cancer risk: a meta-analysis. *Int J Cancer* 2003;**107**:1023–9.
8. Petticrew M, Fraser JM, Regan MF. Adverse life-events and risk of breast cancer: a meta-analysis. *Br J Health Psychol* 1999;**4**:1–17.
9. Garssen B. Psychological factors and cancer development: evidence after 30 years of research. *Clin Psychol Rev* 2004;**24**:315–38.
10. McGee R. Does stress cause cancer? There's no good evidence of a relation between stressful events and cancer. *BMJ* 1999;**319**:1015–6.
11. Macleod J, Davey Smith G, Heslop P, Metcalfe C, Carroll D, Hart C. Are the effects of psychosocial exposures attributable to confounding? Evidence from a prospective observational study on psychological stress and mortality. *J Epidemiol Commun Health* 2001;**55**:878–84.
12. Macleod J, Davey Smith G, Heslop P, Metcalfe C, Carroll D, Hart C. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. *BMJ* 2002;**324**:1247–51.
13. Heslop P, Davey Smith G, Carroll D, Macleod J, Hyland F, Hart C. Perceived stress and coronary heart disease risk factors: the contribution of socio-economic position. *Br J Health Psychol* 2001;**6**:167–78.
14. Hsing AW. Hormones and prostate cancer: what's next? *Epidemiol Rev* 2001;**23**:42–58.
15. Davey Smith G, Hart C, Blane D, Gillis C, Macleod J, Hawthorne V. Lifetime socioeconomic position and mortality: prospective observational study. *BMJ* 1997;**314**:547–52.
16. Davey Smith G, Hart C, Blane D, Hole D. Adverse socioeconomic conditions in childhood and cause specific adult mortality: prospective observational study. *BMJ* 1998;**316**:1631–5.
17. Reeder LG, Chapman JM, Coulson AH. Socioenvironmental stress, tranquilizers and cardiovascular disease. *Proc Excerpta Med Int* 1968;**182**:226–38.
18. Metcalfe C, Davey Smith G, Wadsworth E, et al. A contemporary validation of the Reeder Stress Inventory. *Br J Health Psychol* 2003;**8**:83–94.
19. OPCS. *Classification of occupations 1966*. London: HMSO; 1966.
20. Carstairs V, Morris R. *Deprivation and health in Scotland*. Aberdeen: Aberdeen University Press; 1991.
21. Hart CL, Davey Smith G, Hole DJ, Hawthorne VM. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of scottish men with 21 years of follow up. *BMJ* 1999;**318**:1725–9.
22. Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. *Biometrika* 1980;**67**:145–53.
23. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer: Collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 2002;**87**:1234–45.
24. MacMahon B. Epidemiology and the causes of breast cancer. *Int J Cancer* 2006;**118**:2373–8.
25. Gunnell D, Okasha M, Davey Smith G, Oliver SE, Sandhu J, Holly JMP. Height, leg length, and cancer risk: a systematic review. *Epidemiol Rev* 2001;**23**:313–42.
26. Okasha M, McCarron P, Gunnell D, Davey Smith G. Exposures in childhood, adolescence and early adulthood and breast cancer risk: A systematic review of the literature. *Breast Cancer Res Treat* 2003;**78**:223–76.
27. Grönberg H. Prostate cancer epidemiology. *Lancet* 2003;**361**:859–64.
28. Kreuz LE. Suppression of plasma testosterone levels and psychological stress – longitudinal study of young men in officer candidate school. *Arch Gen Psychiat* 1972;**26**:479–82.
29. Rose RM. Androgen responses to stress. 2. Excretion of testosterone, epitestosterone, androsterone and etiocholanolone during basic combat training and under threat of attack. *Psychosom Med* 1969;**31**:418–36.