Blood Pressure and Cancer in Middle-Aged British Men

GOYA WANNAMETHEE AND A G SHAPER

Wannamethee G (Department of Public Health, Royal Free Hospital School of Medicine, Rowland Hill St, London NW3 2PF, UK) and Shaper A G. Blood pressure and cancer in middle-aged British men. International Journal of Epidemiology 1996; 25: 22–31.

Background. This paper examines the relationship between blood pressure and cancer mortality.

Methods. A prospective study of 7735 middle-aged men drawn at random from one general practice in each of 24 British towns.

Results. During a mean follow-up period of 12.75 years there were 351 deaths from cancers. The relationship between blood pressure and cancer differed with respect to follow-up period. In the first 5 years of follow-up, a significant inverse relationship was seen between systolic (SBP) and diastolic blood pressure (DBP) and cancer mortality even after adjustment for age, smoking, social class, physical activity, alcohol intake, body mass index, diabetes, pre-existing ischaemic heart disease, use of antihypertensive drugs, cholesterol, heart rate and serum albumin. In the subsequent follow-up period (5.1–12.75 years) a significant positive association was seen between SBP (but not DBP) and risk of cancer mortality, even after adjustment for the other risk factors. Men in the top fifth of SBP (>161 mmHg) showed over a 50% increase in risk of cancer mortality compared to men in the bottom quintile (RR = 1.56 95% CI : 1.04–2.38). This positive relationship between SBP and cancer was seen only in current cigarette smokers. Use of antihypertensive drugs was not associated with cancer mortality.

Conclusion. The association of elevated SBP with increased risk of cancer mortality seen only in current smokers warrants the search for factors which affect SBP, interact with smoking and are potentially carcinogenic.

Keywords: systolic blood pressure, smoking, cancer mortality

The suggestion that blood pressure may be associated with increased risk of cancer first aroused interest nearly two decades ago. Dyer et al. reported a relationship between blood pressure and all-cancer mortality independent of age, smoking and cholesterol.1 Since then several prospective studies have examined this relationship but the findings have been inconsistent. Some studies have reported a positive association,2–6 others have reported no association7,8 and some have reported increased risk of cancer mortality in the low blood pressure group in the elderly.9,10 In two studies reporting a positive association the relationship was specific to certain sites3,5 and it has also been suggested that the blood pressure-cancer relationship may be an indirect result of other aetiological factors e.g. alcohol and dietary factors.3 The relationship appears to vary with respect to length of follow-up3 and age-group9 and although it has been observed that the relationship becomes stronger with longer follow-up,3 previous investigators have not clearly distinguished between early and late deaths in order to take into account the possible effects of preclinical cancer on blood pressure. We have examined the relationship between systolic (SBP) and diastolic blood pressure (DBP) and cancer mortality in 7735 middle-aged British men followed for a mean period of 12.75 years with particular focus on time from blood pressure measurement to death and on possible confounding factors.

MATERIALS AND METHODS

The British Regional Heart Study (BRHS) is a prospective study of cardiovascular disease involving 7735 men aged 40–59 years selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales and Scotland. The criteria for selecting the town, the general practice and the subjects as well as the methods of data collection have previously been reported.11 In brief, the 24 towns were primarily selected from those with populations of about 50 000–100 000 (1971 Census), to represent the full range of cardiovascular mortality and to include all major standard regions. One general practice in each town was selected primarily to reflect the social class distribution of men in that town. From each age-sex
register about 420 men aged 40–59 years were selected at random to produce 5-year age groups of equal size. An average response rate of 78% was achieved. Research nurses administered to each man a standard questionnaire which included questions on smoking habits, alcohol intake and medical history. Several physical measurements were made, and blood samples were taken for measurement of biochemical and haematological variables. The men were classified according to their current smoking status: those who had never smoked, ex-cigarette smokers and current smokers at four levels (1–19, 20, 21–39 and ≥40 cigarettes/day). Those who had only ever smoked pipe/cigars are grouped as ‘never smoked’. Ex-cigarette smokers who are currently pipe/cigar smokers are classified as ex-cigarette smokers.

Alcohol consumption was recorded using questions on frequency, quantity and type, similar to those used in the 1978 General Household Survey. The men were classified into five drinking categories on the basis of their estimated weekly intake: none (0), occasional (<1 unit/week), light (1–15 units/week), moderate (16–42 units/week) and heavy (>42 units/week—i.e. more than six drinks daily). The longest-held occupation of each man was recorded and then coded in accordance with the Registrar General’s occupational classification into six social class groups: I, II, III non-manual or III manual, IV or V. Men whose longest occupation had been in the Armed Forces form a separate group. Body mass index (BMI) calculated as weight/height²; was used as an index of relative weight. Heart rate was measured from the resting electrocardiogram. The men were asked to indicate their usual pattern of physical activity which included regular walking or cycling, recreational activity and sporting (vigorous) activity. A physical activity (exercise) score was derived for each man based on frequency and type (intensity) of the physical activity. The men were grouped into six broad categories based on their total score: inactive, occasional, light, moderate, moderately vigorous and vigorous.

Pre-existing Disease
The men were asked to recall a doctor’s diagnosis of angina, myocardial infarction, stroke, diabetes, bronchitis, asthma, peptic ulcer and a number of other disorders listed on the questionnaire. They were also asked details of any regular medical treatment including use of antihypertensive drugs. The WHO (Rose) chest pain questionnaire was administered to all men at the initial examination and a three-orthogonal lead electrocardiogram (ECG) was recorded at rest.

Ischaemic Heart Disease
Men with pre-existing evidence of ischaemic heart disease (IHD) consist of those with electrocardiographic evidence of possible/definite myocardial ischaemia or possible/definite myocardial infarction, those with angina or possible myocardial infarction on WHO chest pain questionnaire and those with recall of a doctor diagnosis of angina or myocardial infarction.

Blood Pressure
The men attended the examination centre over a 10-hour period between 8.30 a.m. and 6.30 p.m. on weekdays and were not asked to fast or to abstain from alcohol beforehand. The London School of Hygiene sphygmanometer was used to measure blood pressure twice in succession with the subjects seated and the arm supported on a cushion. The mean of the two readings was used in the analysis and all blood pressure readings were adjusted for observer variation within each town.

Follow-up
All men, whether or not they showed evidence of IHD at initial examination were followed up for all-cause mortality and cardiovascular morbidity.

Information on death was collected through the established ‘tagging’ procedures provided by the NHS registers in Southport (for England and Wales) and Edinburgh (for Scotland). Classification into deaths from cardiovascular and non-cardiovascular causes was based on the International Classification of Diseases 9th Revision codings on the death certificates.

STATISTICAL METHODS
Direct standardization was used to obtain age-adjusted rates/1000 person-years using the study population as the standard. Cox’s proportional hazards model was used to assess the relation between blood pressure and cancer mortality and to obtain relative risks adjusting for the other risk factors. The relative risk for the five SBP groups adjusted for the coronary risk factors was obtained fitting SBP as four dummy variables (for the five SBP groups). Tests for trend were assessed fitting SBP as a continuous variable. In the adjustment, age and heart rate were fitted continuously. Blood cholesterol was fitted as six categorical variables based on the distribution of cholesterol (<4.8, 4.8–, 5.5–, 6.0–, 6.5–, ≥7.2 mmol/l). The six groups are based on fifths of the distribution with the lowest fifth subdivided because of the reported association between low cholesterol and cancer. Body mass index was fitted as six categorical
Table 1  Crude and age-adjusted mean systolic (SBP) and diastolic blood pressure (DBP) in men alive at end of study period and in men who died of cancer

<table>
<thead>
<tr>
<th></th>
<th>Alive (6/09)</th>
<th>All (351)</th>
<th>&lt;5 years (82)</th>
<th>&gt;5 years (269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>144.3 (0.3)</td>
<td>148.4 (1.2)**</td>
<td>142.8 (2.4)</td>
<td>150.1 (1.4)**</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>144.6 (0.3)</td>
<td>146.2 (1.1)</td>
<td>140.7 (2.3)*</td>
<td>147.9 (1.3)**</td>
</tr>
<tr>
<td>Mean DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>82.0 (0.2)</td>
<td>81.8 (0.7)</td>
<td>79.3 (1.4)*</td>
<td>82.5 (0.8)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>82.1 (0.2)</td>
<td>81.4 (0.7)</td>
<td>79.0 (1.5)*</td>
<td>82.1 (0.8)</td>
</tr>
<tr>
<td>% antihypertensive treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>3.8</td>
<td>4.6</td>
<td>4.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>4.1</td>
<td>3.7</td>
<td>4.1</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Comparisons with men still alive at last follow-up period.
*** P < 0.0001, ** P < 0.001, * P < 0.05, + 0.05 < P < 0.08.

variables based on the levels of BMI (<20, 20–22, 22–24, 24–26, >28 kg/m²) as a non-linear relationship has been observed between BMI and mortality. Use of antihypertensive drugs and the presence of IHD were fitted as 0,1 variables, alcohol as four dummy variables for the five alcohol groups, social class as six dummy variables for the seven social class groups and physical activity as five dummy variables for the six physical activity categories. Adjustment for smoking status and quantity smoked was carried out fitting smoking as five dummy variables for the six levels of smoking categories. The adjusted relative risk for SBP by smoking status in Figure 2 was assessed by fitting smoking-SBP interaction terms in the model with all current cigarette smokers combined. To test whether the ratio of hazards depends on time, a time-dependent explanatory variable \( X = X(t) \), where \( X(t) = \log(t) \) * blood pressure, was fitted in the model. At each event time, subjects still alive just before each event time, will have their X value changed accordingly.

RESULTS
During a mean follow-up period of 12.75 years (range 11.5–14.0 years) there were 1018 deaths from all causes including 351 deaths (34%) from cancer, 519 (51%) from cardiovascular causes and 148 (15%) from other non-cardiovascular causes. Table 1 shows the mean SBP and DBP and the proportion of men on antihypertensive therapy at initial examination in those who had died of cancer and in men who were alive by the end of the study period (December 1991). In the whole study period, men who died of cancer showed significantly higher SBP than those still alive (\( P = 0.0003 \)) but the difference was attenuated after adjustment for age. No significant difference was seen for DBP. Since pre-clinical cancer may be associated with changes in blood pressure and may result in death early in the follow-up, cancer deaths were divided into those which occurred within 5 years of initial examination for each man and those which occurred subsequently (>5 years). Mean SBP in cancer deaths occurring within the first five years was slightly lower than in men who were alive and significantly lower than in deaths occurring later in follow-up. Mean SBP in deaths occurring after 5 years from blood pressure measurement was significantly higher than in men still alive (\( P < 0.0001 \)) even after adjustment for age (\( P = 0.008 \)). Mean DBP in cancer deaths in the first 5 years was lower than in men still alive and this was significant after adjustment for age. Unlike SBP no difference was seen in mean DBP between later deaths and men still alive. At initial examination, 375 men were on antihypertensive treatment and the data suggested that the use of antihypertensive drugs was not associated with cancer mortality.

Time of Follow-Up
We have examined the relationship between blood pressure and cancer rates/1000 person-years by equal fifths of the ranked SBP and DBP distribution. When all cancer deaths in the follow-up period were included, a significant positive association was seen between SBP and cancer mortality which was reduced to non-significance after adjustment for age (Figure 1A).
When the relationship was examined by period of follow-up, an inverse association was seen in the first 5 years (Figure 1B) which was significant after adjusting for age (regression coefficient $b = -0.01$; $P = 0.05$), and a significant positive association was seen when early deaths (<5 years) were excluded (Figure 1C). The positive relationship remained significant even after age-adjustment (regression coefficient $b = 0.006$; $P = 0.02$). A test to assess whether the SBP-cancer relationship varied with time of follow-up was significant ($P = 0.01$). When deaths occurring in the later follow-up period (Figure 1C) are further separated into two approximately equal time periods (5–9 and >9 years), a positive association was seen in both periods (data not shown). No significant interaction with time was found in the follow-up period 5.1–12.75 years. Therefore, in all subsequent analyses, attention is focused on the relations between SBP and cancer in the two main time periods, i.e. first 5 years after screening and the subsequent 7.75 years.

For DBP no association was seen for all cancer deaths in the whole study period (Figure 2A). When divided by period of follow-up a significant inverse association was seen in the early follow-up period (regression coefficient $b = -0.02$; $P = 0.03$) (Figure 2B) but unlike SBP no association was seen in the subsequent follow-up period (Figure 2C).
Possible Confounding Factors
In order to assess the independent contribution of SBP to cancer mortality, we have examined the relationship adjusting for factors known to be associated with cancer or all-cause mortality, i.e. age, social class, smoking, alcohol intake, physical activity, use of antihypertensive treatment, presence of pre-existing IHD, diabetes, total cholesterol and BMI as well as heart rate and albumin, two factors shown previously to be associated with SBP and cancer mortality in this study population. Factors related to all-cause mortality have been included because of the issue of competing mortality from cardiovascular cases.

First Five Years of Follow-Up
Table 2 shows the relationships between SBP and cancer mortality in the first 5 years of follow-up. Adjustment for the above confounding factors made little difference to the inverse association seen between SBP and cancer and the trend was of marginal significance \((P = 0.07)\). The inverse association with DBP seen in the first 5 years remained significant after these adjustments \((P = 0.03)\). The relative risk and 95% confidence limits for the fifths of DBP after adjustment for the other confounding factors were 1.00, 0.57 \((0.29, 1.12)\), 0.68 \((0.53, 1.27)\), 0.56 \((0.28, 1.11)\) and 0.36 \((0.17, 0.77)\).
antly with increasing SBP (P = 0.001). Men in the top mortality. Risk of cancer mortality increased significantly with risk factors which are more likely to predispose to cardiovascular mortality, e.g. diabetes, total cholesterol, body mass index, heart rate and serum albumin.

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>No of deaths</th>
<th>Age-adjusted RR</th>
<th>95% confidence interval</th>
<th>Adjusted* RR</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;128</td>
<td>22</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>128–</td>
<td>14</td>
<td>0.69</td>
<td>0.35–1.36</td>
<td>0.63</td>
<td>0.32–1.30</td>
</tr>
<tr>
<td>138–</td>
<td>21</td>
<td>0.90</td>
<td>0.50–1.65</td>
<td>0.91</td>
<td>0.51–1.77</td>
</tr>
<tr>
<td>148–</td>
<td>10</td>
<td>0.41</td>
<td>0.20–0.89</td>
<td>0.39</td>
<td>0.18–0.85</td>
</tr>
<tr>
<td>161–</td>
<td>15</td>
<td>0.52</td>
<td>0.27–1.00</td>
<td>0.50</td>
<td>0.25–1.00</td>
</tr>
</tbody>
</table>

| regression coefficient b = -0.01 | b = -0.01 |
| test for trend P = 0.05 | P = 0.07 |

*Adjusted for age, social class, smoking, alcohol intake, physical activity, use of antihypertensive drugs, pre-existing ischaemic heart disease, diabetes, total cholesterol, body mass index, heart rate and serum albumin.

Exclusion of Early Follow-Up
Table 3 shows the age-adjusted relative risk of cancer mortality by fifths of SBP for the period from 5.1 to 12.75 years, and the relative risk adjusted for confounding factors as in Table 2. As low blood pressure is associated with higher rates of low cholesterol and leanness, factors shown to be associated with increased cancer mortality and as elevated SBP is associated with risk factors which are more likely to predispose to cardiovascular mortality, e.g. diabetes and pre-existing IHD, adjustment for the above factors has strengthened the relationship between elevated SBP and cancer mortality. Risk of cancer mortality increased significantly with increasing SBP (P = 0.001). Men in the top fifth showed over a 50% increase in risk of cancer mortality compared to men in the bottom quintile.

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>No of deaths</th>
<th>Age-adjusted RR</th>
<th>95% confidence interval</th>
<th>Adjusted* RR</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;128</td>
<td>40</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>128–</td>
<td>43</td>
<td>1.17</td>
<td>0.77–1.79</td>
<td>1.14</td>
<td>0.73–1.77</td>
</tr>
<tr>
<td>138–</td>
<td>57</td>
<td>1.39</td>
<td>0.93–2.08</td>
<td>1.42</td>
<td>0.93–2.11</td>
</tr>
<tr>
<td>148–</td>
<td>62</td>
<td>1.46</td>
<td>0.98–2.16</td>
<td>1.53</td>
<td>1.01–2.31</td>
</tr>
<tr>
<td>161–</td>
<td>67</td>
<td>1.38</td>
<td>0.92–2.04</td>
<td>1.56</td>
<td>1.04–2.38</td>
</tr>
</tbody>
</table>

| regression coefficient b = 0.006 | b = 0.009 |
| test for trend P = 0.02 | P = 0.001 |

*Adjusted for age, social class, smoking, alcohol intake, physical activity, use of antihypertensive drugs, pre-existing ischaemic heart disease, diabetes, total cholesterol, body mass index, heart rate and serum albumin.

Specific Sites
When early deaths were excluded mean SBP was significantly higher in lung cancer deaths (n = 85) than in men still alive (148.6 versus 144.6; P = 0.05). In the later follow-up period mean SBP at screening was also higher in oesophagus (n = 17), colon (n = 19) and bladder (n = 13) cancer deaths compared to men still alive but these differences were not statistically significant at the 5% level, possibly because of small numbers.

Smoking, Systolic Blood Pressure and Cancer Mortality
The higher levels of SBP observed in those dying in the later follow-up period of lung, bladder, oesophagus and colon cancer, cancers which are associated with smoking, suggest that the relationship between SBP and cancer may be due to some interaction between SBP, smoking and cancer. The relationship between SBP and cancer has been examined separately in current and non-current cigarette smokers, excluding deaths occurring within 5 years of follow-up and adjusting for the other confounding risk factors (Figure 3). The positive association with all-cancer mortality was seen only in current cigarette smokers, in whom the risk of cancer mortality increased significantly (test for trend; P < 0.0001). The relationship between number of cigarettes smoked per day and mean SBP was weak (144.3, 145.0, 145.3 and 144.3 mmHg respectively for the four levels of smoking: 1–19, 20, 21–39 and ≥40 cigarettes/day). The proportion of heavy smokers (≥21 cigarettes/day) did not vary significantly among the five SBP groups (33%, 38%, 36%, 40% and 36% respectively), although the prevalence was lowest in the lowest fifth of SBP (<128 mmHg). Thus further adjustment for number of cigarettes smoked per day reduced the increased risk only slightly and the trend remained significant (P < 0.0001). No association was seen between SBP and cancer mortality in non-current cigarette smokers. When non-current cigarette smokers were separated into those who had never smoked and ex-smokers, no association was seen in either group. A test for interaction confirmed a significant difference in the SBP-cancer mortality relationship by current smoking status (P = 0.02).

Lung and Other Cancers
We have also examined the relationship for lung cancer and the other cancer sites in smokers and non-smokers adjusting for the other risk factors listed in Table 2. The positive association with SBP was seen for both lung
Adjusted Relative Risk of Cancer Mortality

No. of men

Current
Non-smoker

Current
Non-smoker

<128 128- 138- 148- 161-

FIGURE 3 Adjusted (+) relative risk of all-cancer mortality by fifths of systolic blood pressure according to current cigarette smoking status, excluding all deaths occurring within 3 years of follow-up. Number of deaths indicated on Figure.

(+): Adjusted for age, social class, alcohol intake, physical activity, use of antihypertensive drugs, pre-existing ischaemic heart disease, diabetes, total cholesterol, body mass index, heart rate and serum albumin.

cancer and other cancers in smokers (Figure 4). No association was seen in non-smokers. Further adjustment for quantity of cigarettes smoked reduced the increased risks slightly but the trends remained significant ($P = 0.002$ and $P = 0.0006$ respectively).

DISCUSSION

Since the initial suggestion that blood pressure may be a risk factor for cancer, several population studies have examined the relationship between blood pressure and risk of cancer and the findings have been inconsistent. These studies vary considerably with respect to sampling, from general population cohorts to employed groups, elderly groups and hypertensive subjects. The groups vary considerably by age and sex distribution and by period of follow-up. Only one study has examined the blood pressure-relationship by time of follow-up. These differences almost certainly account for the inconsistent outcomes. However, in most studies in middle-aged cohorts with longer follow-up, a positive association between SBP and cancer mortality has been observed. In the present study the blood pressure relationship was dependent on time of follow-up from initial measurement and a significant interaction was seen with time. A significant inverse relationship was seen for both SBP and DBP with cancer deaths that occurred within 5 years from initial blood pressure measurement. When early deaths were excluded, a significant positive association was seen, with risk of cancer increasing progressively with increasing SBP even after adjustment for other potential confounding factors. No association was seen with DBP. These findings are similar to those of the Western Electric Study in which men in a similar age group were examined and similar follow-up periods were used in the analysis. They observed no relationship between SBP and cancer in the first 5 years and a positive association which was strongest in the 12-17 year follow-up period. No data were presented for DBP.

Blood Pressure and Early Deaths

Presence of preclinical cancer is usually associated with loss of weight which may be accompanied by a fall in blood pressure, and weight loss and thinness have been shown to be strongly associated with increased risk of cancer deaths. The inverse association seen between blood pressure and cancer deaths within a 5-year follow-up is probably due to chronic ill-health or preclinical cancer at screening. Similar results have also been observed in a 5-year follow-up of elderly subjects in three US communities and in the subgroup of men and women aged over 70 from the Copenhagen Heart Study followed for 10 years. The increased risk of cancer in the low blood pressure groups which have been observed particularly in the elderly, in whom cancer is more prevalent, is likely to be associated with ill-health.

Specific Cancer Sites

This study was not designed to examine site-specific cancer but the positive relationship with SBP was most clearly seen for lung cancer, as well as for oesophagus, colon and bladder cancer, all of which are associated with cigarette smoking. Some studies have found positive associations between hypertension and renal cancer and between cerebrovascular disease and stomach cancer. The number of deaths from renal cancer and stomach cancer in the present study was small but a positive association (non-significant) was seen with stomach cancer.
Synergistic Effect of Smoking
The association of SBP with smoking-related cancers suggested that the relationship may be linked with smoking. Although the relationship persisted after adjusting for smoking in a multivariate model this does not take into account any possible synergistic effect with smoking. When examined separately in current cigarette smokers and non-smokers a significant and strongly positive association was seen only in smokers. This was present for both lung and other cancers although it was most marked for lung cancer. We are not aware of any previous study that has stratified the relationship by smoking status. Systolic blood pressure is not a proxy for smoking as the relationship between smoking and SBP is weak in this cohort. White blood cell count is strongly associated with smoking and is correlated with SBP and has been shown to be strongly predictive of lung cancer. However, further adjustment for white blood cell count made little difference to the relationships seen.

Confounding Biases
Although statistical adjustments were made for lifestyle factors, it is possible that a raised SBP may simply be a marker for lifestyle factors which increase the risk of cancer and are not completely accounted for by the limited statistical procedures. We have explored this possibility by determining, in both smokers and non-smokers, the distribution of heavy drinking, the proportion of manual workers and the mean serum total cholesterol in the fifths of the SBP by current smoking status. Both smokers and non-smokers showed the same pattern of increasing levels of these risk factors with increasing SBP although no association was seen between SBP and cancer in non-smokers. Further, although there were differences in the distribution of risk factors seen in the smokers by fifths of SBP, they were relatively small and are unlikely to explain the significant increase in risk seen only in smokers.

The possibility that those who drink heavily or smoke heavily may not admit to such behaviour has also been considered. In this study we have already shown, using 25 biochemical and haematological variables that the reported alcohol intake levels are valid on a group basis. Cadmium levels in this cohort have been shown to relate strongly to smoking levels and there is little difference in mean cadmium levels between the fifths of SBP distribution in smokers. There seems to be no evidence that those with higher SBP are heavier smokers, which is consistent with the reported data.

Town of residence has been shown to be an important predictor of blood pressure in this cohort. Although cancer mortality is strongly associated with heavy smoking on a town basis there is no relationship between cancer mortality and town mean SBP. Thus
adjustment for town of residence in the multivariate analysis model made little difference to the overall relationship between SBP and cancer mortality in smokers.

**Mechanisms**

The nature of the relationship between SBP and cancer is uncertain but in this study it appears to increase susceptibility to cancer only in the presence of smoking. It has been suggested that the relationship may be a consequence of common aetiological factors, e.g. dietary factors and alcohol. In the present study, the positive association with cancer persisted after adjustment for alcohol intake. Salt intake is associated with blood pressure and has been shown to be associated with stomach cancer. The positive association seen with stomach cancer may be explained by dietary factors but the frequency of stomach cancer in this study is low and salt intake is unlikely to explain the overall association observed.

It has been suggested that use of antihypertensive treatment may be carcinogenic and associated with increased cancer risk, particularly renal cancer. In the present study the number of renal cancers was very small but use of antihypertensive treatment showed no relationship with overall cancer mortality, consistent with other studies. The SBP cancer relationship is thus unlikely to be explained by antihypertensive treatment. It has also been suggested that certain cancers may result in raised blood pressure and that the higher incidence in hypertensives is a consequence of cancer. This seems unlikely in the present study because the positive association was stronger after exclusion of early deaths. It was suggested that the relationship may be due to common biological factors relating to both SBP and cancer risk. We have examined three possible biological confounders (heart rate, albumin and white cell count), none of which explained the positive association seen.

**Systolic and Diastolic Blood Pressure**

The significant inverse relationship between blood pressure and cancer mortality in the first 5 years of follow-up, is similar for both SBP and DBP. If this phenomenon is due to preclinical cancer or other underlying ill-health, this is what would be expected. However, the specificity of the positive relationship between SBP and cancer mortality in the subsequent period of follow-up in the present study suggests an explanation that involves predominantly SBP. The specific association with SBP but not DBP has been observed in two other studies. This study cannot provide an answer to this issue of causality, but we can draw attention to the multiplicity of factors affecting and possibly initiating increases in SBP and DBP. While SBP and DBP are strongly correlated (r = 0.7) in the British Regional Heart Study cohort, at every level of SBP there is a very wide range of DBP and vice versa. It is very likely that some factors contributing to essential hypertension in humans have a differential effect on SBP and DBP.

**Implications**

Dyer et al. suggested that SBP may be a risk factor for cancer and the findings of the present study do not refute this hypothesis. The strong interaction with time and the interaction with smoking observed in the present study may explain the inconsistencies observed between reported studies. Further studies are required to examine the SBP-cancer relationship taking period of follow-up into account and to examine the relationship separately in current cigarette smokers and in non-cigarette smokers. If the findings in this study are confirmed, a search should be made for factors which particularly affect SBP, interact with smoking and are potentially carcinogenic.

**ACKNOWLEDGEMENTS**

The British Regional Heart Study is a British Heart Foundation Research Group and receives support from the Department of Health.

**REFERENCES**


(Revised version received June 1995)