Short Communication
Blood pressure and renal cancer risk: the HUNT Study in Norway

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In a prospective study of 36 728 women and 35 688 men during 18 years of follow-up, compared to systolic pressure < 130 mm Hg, levels of 130–149, 150–169 and ≥ 170 mm Hg in women were associated with relative risks of renal cell cancer of 1.7, 2.0 and 2.0, respectively (P for linear trend, 0.11). In men, there was no association with blood pressure.

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The association of blood pressure with risk of renal cell cancer has been investigated in a number of cohort (Fraser et al, 1990; Grove et al, 1991; Coughlin et al, 1997; Heath et al, 1997; Chow et al, 2000; Choi et al, 2005; Flaherty et al, 2005; Fryzek et al, 2005; Lindgren et al, 2005; Schouten et al, 2005) and case–control (McLaughlin et al, 1995; Yuan et al, 1998; Shapiro et al, 1999) studies, using as principal exposure variable either recorded blood pressure or reported hypertension. In men, recorded blood pressure has shown a convincing exposure–response gradient related to renal cell cancer risk (Coughlin et al, 1997; Chow et al, 2000). In women, however, only reported history of hypertension has been studied as the main exposure variable. In one cohort (Flaherty et al, 2005) and two case–control studies (Yuan et al, 1998; Shapiro et al, 1999), history of hypertension was associated with increased risk. Documenting the presence or the lack of an exposure–response gradient in women is important, and might promote a better probing of the underlying mechanism of the association.

In this prospective study of 36 728 women and 35 688 men with renal cell cancer risk during 18 years of follow-up, together with related to ever use of blood pressure medication.

MATERIALS AND METHODS
In 1984, 85 100 individuals were invited to the Nord Trøndelag Health Study (the HUNT Study) in Norway, and 75 058 (88.2 percent) accepted the invitation, filled in a self-administered questionnaire, and attended a clinical examination until the diagnosis of renal cell cancer or other cancers (except basal cell carcinoma), death from other causes, or the end of follow-up, 31 December 2002, whichever came first. The relative risk was calculated as the rate of renal cell cancer within a given blood pressure category compared with that related to ever use of blood pressure medication.

Body mass index was calculated as weight (in kg) divided by the squared value of height (in metres), and grouped into four categories: < 18.5, 18.5–24.9, 25–29.9 and ≥ 30. Information on smoking was categorised as never, former or currently smoking. Education was divided into three categories, depending on duration (< 9, 10–12 and > 12 years).

The mandatory reporting of cancer by physicians and hospitals to the Cancer Registry of Norway (www.kreftregisteret.no) provides information on incident cases of renal cell cancer that occurred during follow-up. Person-years were calculated from the clinical examination until the diagnosis of renal cell cancer or other cancers (except basal cell carcinoma), death from other causes, or the end of follow-up, 31 December 2002, whichever came first. The relative risk was calculated as the rate of renal cell cancer within a given blood pressure category compared with that in the reference category. We used Cox regression analysis to adjust for potential confounding by body mass index, smoking, use of blood pressure medication and education level. The statistical analyses were conducted using STATA, version 9.0 (StataCorp LP, 1985–2005).

RESULTS
During 18 years of follow-up, 94 women and 144 men were diagnosed with renal cell cancer. Characteristics of the cohort are shown in Table 1. Risk was much lower in women with systolic pressure below 130 mm Hg than for those with higher levels, after adjustment for age, body mass index, smoking status, use of blood pressure medication and education (Table 2). Compared to the reference (< 130 mm Hg), the adjusted relative risk in women with systolic pressure 130–149 mm Hg was 1.7 (95% confidence interval (CI), 0.9–3.5), with levels 150–169 mm Hg the risk was 2.0 (95%
CI, 0.9 – 4.2), and with levels ≥ 170 mm Hg, it was 2.0 (95% CI, 0.9 – 4.6). For diastolic pressure, the association with renal cancer risk was weaker than for systolic. Compared to the reference (< 85 mm Hg), the adjusted relative risk in women with diastolic pressure ≥ 105 mm Hg was 1.6 (95% CI, 0.8 – 3.5).

In a separate analysis restricted to people who reported never-use of blood pressure medication at baseline, there was a strong and positive association between systolic pressure and risk among women (Table 3). Thus, the adjusted relative risk in women with systolic pressure ≥ 170 mm Hg compared with < 130 mm Hg was 3.4 (95% CI, 1.3 – 8.9), and it showed a significant trend with increasing systolic pressure (P for trend, 0.001); diastolic pressure among never users of blood pressure medication, however, showed similar associations to the overall results.

Use of antihypertensive medication, as reported by women at baseline, showed a weak positive association (adjusted relative risk, 1.4, 95% CI, 0.8 – 2.2, Table 2). In men, there was no clear association with systolic or diastolic blood pressure (Tables 2 and 3), and none between blood pressure medication and risk (Table 2).

**DISCUSSION**

The most striking finding in this study was that nonmotive systolic blood pressure among women (< 130 mm Hg) was associated with consistently lower risk for renal cell cancer than higher levels. No previous study of women has assessed the effect of measured blood pressure on this risk, but a positive association with recorded blood pressure has been found among men (Coughlin et al, 1997; Chow et al, 2000).

Correspondingly, studies of antihypertensive medication, or history of hypertension, have not shown consistent results. In two prospective studies, antihypertensive treatment was associated with higher risk of renal cell cancer (Fraser et al, 1999; Heath et al, 1997), but others found no association (Grove et al, 1991; Flaherty et al, 2005; Schouten et al, 2005). One large study linking prescriptions and cancer registration in Denmark indicated that antihypertensive medication may increase risk, but was interpreted as being due to confounding by underlying hypertension (Fryzek et al, 2005). One prospective study (Flaherty et al, 2005) and two case–control studies (Yuan et al, 1998; Shapiro et al, 1999) have also reported positive associations with a history of hypertension.

Contrary to previous evidence, we found that measured blood pressure, or use of blood pressure medication, was not associated with risk for renal cell cancer among men. The reason for this discrepancy is not obvious, but may be the play of chance.

In our study, systolic and diastolic blood pressures were measured according to standardised procedures by a team of trained nurses. The cohort consists of the majority of adults in a stable, homogeneous population in Norway, well suited for cancer

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**Table 1** Characteristics of the study population (36,728 women and 35,688 men), stratified by systolic blood pressure categories

| Characteristic          | No. of participants | No. of renal cell cancers | Median person years (range) | Mean age at diagnosis, years (s.d.) | No. of renal cell cancers | No. of participants | Median person years (range) | Mean age at diagnosis, years (s.d.) |
|-------------------------|----------------------|---------------------------|----------------------------|-------------------------------------|---------------------------|----------------------|----------------------------|-------------------------------------|
|                         | <130                 | 13                        | 18 (19)                    | 60 (15)                             | 13                        | 745                  | 18 (19)                    | 60 (15)                             |
|                         | 130–149              | 26                        | 18 (19)                    | 72 (12)                             | 17 (19)                   | 9251                 | 18 (19)                    | 72 (12)                             |
|                         | 150–169              | 24                        | 17 (19)                    | 73 (13)                             | 13 (19)                   | 5292                 | 17 (19)                    | 73 (13)                             |
|                         | ≥ 170                | 22                        | 13 (19)                    | 79 (9)                              | 7 (10)                    | 4440                 | 7 (10)                     | 79 (9)                              |
|                         |                      |                           |                            |                                     |                          |                      |                            |                                     |
|                         | <130                 | 31                        | 18 (19)                    | 64 (15)                             | 18 (19)                   | 3192                 | 18 (19)                    | 64 (15)                             |
|                         | 130–149              | 40                        | 17 (19)                    | 64 (14)                             | 17 (19)                   | 5954                 | 17 (19)                    | 64 (14)                             |
|                         | 150–169              | 56                        | 13 (19)                    | 73 (9)                              | 10 (19)                   | 3192                 | 10 (19)                    | 73 (9)                              |
|                         | ≥ 170                | 62                        | 7 (10)                     | 79 (8)                              | 8 (10)                    | 3192                 | 8 (10)                     | 79 (8)                              |

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**Table 2** Relative risk of renal cell cancer associated with standardised blood pressure and self reported blood pressure medication

| Variable               | Person years | Cases | RR* | 95% CI | P_trend | Person years | Cases | RR* | 95% CI | P_trend |
|------------------------|--------------|-------|-----|--------|----------|--------------|-------|-----|--------|----------|
| Systolic blood pressure |              |       |     |        |          |              |       |     |        |          |
| <130                   | 304754       | 13    | 1.0 | (Reference) | — | 200863       | 31    | 1.0 | (Reference) | — |
| 130–149                | 145513       | 26    | 1.7 | (0.9–3.5) | — | 223960       | 40    | 0.8 | (0.5–1.4) | — |
| 150–169                | 73828        | 24    | 2.0 | (0.9–4.2) | — | 81183        | 35    | 1.2 | (0.7–2.0) | — |
| ≥ 170                  | 53060        | 22    | 2.0 | (0.9–4.6) | 0.11 | 33890        | 18    | 1.0 | (0.5–1.9) | 0.59 |
| Diastolic blood pressure |              |       |     |        |          |              |       |     |        |          |
| <85                    | 346610       | 31    | 1.0 | (Reference) | — | 264778       | 41    | 1.0 | (Reference) | — |
| 85–94                  | 145246       | 22    | 0.8 | (0.5–1.5) | — | 173219       | 56    | 1.6 | (1.0–2.3) | — |
| 95–104                 | 64349        | 22    | 1.4 | (0.8–2.5) | — | 76975        | 20    | 1.0 | (0.6–1.7) | — |
| ≥ 105                  | 20950        | 10    | 1.6 | (0.8–3.5) | 0.13 | 24924        | 7     | 0.9 | (0.4–2.0) | 0.49 |
| Blood pressure medication |              |       |     |        |          |              |       |     |        |          |
| No                     | 504135       | 57    | 1.0 | (Reference) | — | 499677       | 106   | 1.0 | (Reference) | — |
| Yes                    | 73020        | 28    | 1.4 | (0.8–2.2) | — | 40219        | 18    | 1.1 | (0.6–1.8) | — |

CI = confidence interval, RR = relative risk. *Adjusted for age, blood pressure medication (no, yes), body mass index (< 18.5, 18.5 – 24.9, 25.0 – 29.9, ≥ 30.0), smoking status (never, former, current, unknown), education (< 10, 10–12, ≥ 13 years, unknown). †P-values from trend test using the categories as an ordinal variable in the Cox regression model. ‡Adjusted for age, body mass index (< 18.5, 18.5 – 24.9, 25.0 – 29.9, ≥ 30.0), smoking status (never, former, current, unknown), education (< 10, 10–12, ≥ 13 years, unknown).
follow-up, because of the national mandatory reporting system, and the unique identification number allocated to each citizen.

Angiogenic and other growth factors are associated with blood pressure increase, and may also be involved in the development of renal cell cancer (Schena et al, 1999; Chow et al, 2000; Choueiri et al, 2006). Thus, subtle long-term influences on renal function may lead to hypertension and also be related to tumour growth. The findings raise the possibility that high blood pressure may be a cause of renal cell cancer.

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### Table 3 Relative risk of renal cell cancer associated with standardised measured blood pressure among participants without blood pressure medication

| Variable                             | Women                  | Men                     |
|--------------------------------------|------------------------|-------------------------|
|                                      | Person years | Cases | RR* | 95% CI   | P_trend | Person years | Cases | RR* | 95% CI   | P_trend |
| Systolic blood pressure (mm Hg)      |             |      |     |          |         |             |      |     |          |         |
| <130                                 | 297,321      | 11   | 1.0 | (Reference) | —      | 196,686      | 29   | 1.0 | (Reference) | —      |
| 130–149                              | 125,064      | 17   | 1.8 | (0.8–4.1) | 0.15   | 209,946      | 32   | 0.8 | (0.5–1.3) | 0.2    |
| 150–169                              | 51,547       | 16   | 2.8 | (1.2–6.7) | 0.01   | 68,607       | 29   | 1.3 | (0.7–2.2) | 0.22   |
| 170–189                              | 30,202       | 13   | 3.4 | (1.3–9.9) | 0.005  | 24,437       | 16   | 1.3 | (0.7–2.5) | 0.22   |
| Diastolic blood pressure (mm Hg)     |             |      |     |          |         |             |      |     |          |         |
| <85                                  | 332,154      | 23   | 1.0 | (Reference) | —      | 259,187      | 39   | 1.0 | (Reference) | —      |
| 85–94                                | 118,992      | 16   | 1.1 | (0.6–2.1) | 0.006  | 160,101      | 45   | 1.4 | (0.9–2.2) | 0.008  |
| 95–104                               | 41,705       | 14   | 2.0 | (1.0–4.1) | 0.002  | 62,274       | 16   | 1.1 | (0.6–1.9) | 0.008  |
| 105–109                              | 11,583       | 4    | 1.7 | (0.6–5.0) | 0.08   | 17,199       | 6    | 1.2 | (0.5–2.9) | 0.11   |
| Diastolic blood pressure (per 10 mm Hg increase) | 504,134    | 57   | 1.2 | (1.1–1.3) | 0.001  | 499,676      | 106  | 1.0 | (1.0–1.2) | 0.36   |

CI = confidence interval, RR = relative risk. *Adjusted for age, body mass index (< 18.5, 18.5–24.9, 25.0–29.9, ≥ 30.0), smoking status (never, former, current, unknown), education (< 10, 10–12, ≥ 13 years, unknown). **P-values from trend test using the categories as an ordinal variable in the Cox regression model.