Hypertension and Hormone-Related Neoplasms in Women

Maria Soler, Liliane Chatenoud, Eva Negri, Fabio Parazzini, Silvia Franceschi, Carlo La Vecchia

Abstract—The relation between hypertension and the risk of selected hormone-related neoplasms in women was investigated in a network of case-control studies conducted in Italy during 1983–1996. Cases were women younger than 75 years with histologically confirmed cancer of the breast (n = 3406), endometrium (n = 745), ovary (n = 970), and thyroid (n = 145). Controls were 3054 women admitted in the same geographic area for acute, nonneoplastic, non–hormone-related diseases. Odds ratios (ORs) of treated hypertension were computed after allowance for sociodemographic factors, smoking habits, alcohol consumption, parity, menopausal status, and body mass index (BMI) by means of unconditional logistic regression. The ORs were 1.2 (95% CI, 1.1 to 1.4) for breast cancer and 1.6 (95% CI, 1.3 to 1.9) for endometrial cancer, and the elevated ORs persisted after >5 years since diagnosis of hypertension. No significant association was observed for ovarian and thyroid cancer. For breast cancer, the association was apparently stronger at age 55 years or over and consequently after menopause. No appreciable effect modification was evident for endometrial cancer. Allowance for BMI did not explain the association of postmenopausal breast cancer and endometrial cancer with hypertension. The OR of postmenopausal breast cancer was 1.5 (95% CI, 1.1 to 2.0) in hypertensive women with BMI >30 kg/m^2 compared with normotensive women with BMI <25 kg/m^2. The corresponding figure for all endometrial cancers was 4.9 (95% CI, 3.4 to 6.9). Even in the absence of a clear understanding of biological mechanisms, the definition of a role of hypertension on female hormone–related cancers can have relevant implications on individual risk assessment. (Hypertension. 1999;34:320-325.)

Key Words: hypertension, essential ■ breast neoplasms ■ endometrial neoplasms ■ ovarian neoplasms ■ thyroid neoplasms ■ case-control studies

A possible relation between hypertension or treatment for hypertension and cancer risk has been considered in a few studies dealing with overall cancer mortality. Dyer et al,1 in an American cohort study of 1233 white men, found a relative risk (RR) of 3.0 for total cancer mortality in subjects with a systolic blood pressure >160 mm Hg. Raynor et al,2 in a longitudinal study of 5397 men, found an association (RR = 1.9) between elevated blood pressure and risk of death from all neoplasms. Khaw et al,3 in a 9-year follow-up of a southern California cohort study, found that systolic blood pressure was a significant predictor of subsequent cancer mortality in men, and Goldbourt et al,4 in a cohort of 10 059 middle-aged and elderly men, observed a moderate but significant association between systolic blood pressure and cancer mortality (RR = 1.2). Wannamethee and Shaper,5 in a cohort study of middle-aged British men, considered the relation between the duration of hypertension and total cancer mortality and reported a RR of 1.6 for a systolic blood pressure >160 mm Hg lasting >5 years.

With regard to the possible relation between hypertension and cancer risk in women, specific attention has also been paid to the possible association with breast, endometrial, and ovarian neoplasms.6–29 Available evidence for breast cancer allows exclusion of a strong association with hypertension.7–9 However, the possibility of a moderately increased risk remains open to discussion, mainly for hypertension early in life,7–10 including hypertension in pregnancy. Talamini et al8 found a RR of 2.3 for hypertension in pregnancy in a case-control study. Furthermore, some treatment for hypertension has been associated with breast cancer risk. Armstrong et al,11 Heinonen et al,12 and Stanford et al,13 suggested that rauwolfia derivatives may increase the risk of breast cancer, but other case-control14–16 and cohort studies17 did not support this association. In postmenopausal women, the association between hypertension and breast cancer risk may be partly or largely due to residual confounding by overweight, which is related to both hypertension and postmenopausal breast cancer.7,18

Stronger and more consistent is the relation between hypertension and endometrial cancer risk. Thus, several studies reported a higher risk of the disease in hypertensive women, with odds ratios (ORs) ranging from 1.2 to 2.1.19–28 The association generally persisted after allowance for covariates.27 Because endometrial cancer is strongly related to overweight and obesity, and although most recent studies allowed for measures of body mass index (BMI) in the
analysis, the possibility of some residual confounding by BMI remains open to discussion for this neoplasm as well. Little data exist on the possible relation between hypertension, overweight, and ovarian cancer risk. The RR of ovarian cancer death was 1.6 in obese women in the prospective American Cancer Society One Million Study. Thyroid cancer has also been related to overweight, mainly in postmenopausal women. Consequently, an association with hypertension is possible for this neoplasm as well.

To provide further information on this issue, we systematically analyzed the relation between treated hypertension and cancers of the breast, endometrium, ovarian, and thyroid, with the use of data from a network of case-control studies conducted in Italy.

**Methods**

The data were derived from a network of hospital-based case-control studies conducted in Italy, whose general design has been previously described. All studies followed the same criteria for inclusion and had the same interview setting for cases and controls. Recruitment of cases of various neoplasms and the corresponding controls started during 1983–1985, and the present report is based on data collected

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Breast</th>
<th>Endometrium</th>
<th>Ovary</th>
<th>Thyroid</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>885 (26.0)</td>
<td>48 (6.4)</td>
<td>228 (23.5)</td>
<td>86 (59.3)</td>
<td>886 (29.0)</td>
</tr>
<tr>
<td>46–54</td>
<td>941 (27.6)</td>
<td>137 (18.4)</td>
<td>277 (28.6)</td>
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<td>741 (24.3)</td>
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<tr>
<td>55–64</td>
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<td>65–74</td>
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<td>Greater Milan</td>
<td>2245 (65.9)</td>
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<td>723 (23.7)</td>
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<td>&lt;7</td>
<td>1718 (50.4)</td>
<td>514 (69.0)</td>
<td>557 (57.4)</td>
<td>51 (35.2)</td>
<td>1735 (56.8)</td>
</tr>
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<td>≥7</td>
<td>1684 (49.4)</td>
<td>228 (30.6)</td>
<td>411 (42.4)</td>
<td>93 (64.1)</td>
<td>1315 (43.1)</td>
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<td>2 (0.2)</td>
<td>1 (0.7)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Smoking</td>
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</tr>
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<td>Never</td>
<td>2367 (69.5)</td>
<td>602 (80.8)</td>
<td>731 (75.4)</td>
<td>91 (62.8)</td>
<td>2058 (67.4)</td>
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<tr>
<td>Ex-smokers</td>
<td>270 (7.9)</td>
<td>40 (5.4)</td>
<td>58 (6.0)</td>
<td>16 (11.0)</td>
<td>226 (7.4)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>769 (22.6)</td>
<td>102 (13.7)</td>
<td>181 (18.7)</td>
<td>38 (26.2)</td>
<td>768 (25.1)</td>
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<td>...</td>
<td>2 (0.1)</td>
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<td></td>
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<tr>
<td>Nondrinkers</td>
<td>1006 (29.5)</td>
<td>245 (32.9)</td>
<td>349 (36.0)</td>
<td>56 (38.6)</td>
<td>1160 (38.0)</td>
</tr>
<tr>
<td>&lt;2 drinks/d</td>
<td>1082 (31.8)</td>
<td>224 (30.1)</td>
<td>303 (31.2)</td>
<td>54 (37.2)</td>
<td>924 (30.3)</td>
</tr>
<tr>
<td>≥2 drinks/d</td>
<td>1318 (38.7)</td>
<td>276 (37.0)</td>
<td>318 (32.8)</td>
<td>35 (24.1)</td>
<td>970 (31.8)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>638 (18.7)</td>
<td>161 (21.6)</td>
<td>237 (24.4)</td>
<td>43 (29.7)</td>
<td>675 (22.1)</td>
</tr>
<tr>
<td>1</td>
<td>860 (25.2)</td>
<td>173 (23.2)</td>
<td>204 (21.0)</td>
<td>32 (22.1)</td>
<td>731 (24.0)</td>
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<tr>
<td>≥2</td>
<td>1908 (56.0)</td>
<td>411 (55.2)</td>
<td>526 (54.2)</td>
<td>70 (48.3)</td>
<td>1648 (54.0)</td>
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<tr>
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<td>...</td>
<td>...</td>
<td>3 (0.3)</td>
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<td>...</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-perimenopausal</td>
<td>1221 (35.8)</td>
<td>114 (15.3)</td>
<td>343 (35.4)</td>
<td>86 (59.3)</td>
<td>1024 (33.5)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>2184 (64.1)</td>
<td>631 (84.7)</td>
<td>624 (64.3)</td>
<td>59 (40.7)</td>
<td>2029 (66.4)</td>
</tr>
<tr>
<td>Missing</td>
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<td>...</td>
<td>3 (0.3)</td>
<td>...</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>2129 (62.5)</td>
<td>289 (38.8)</td>
<td>614 (63.3)</td>
<td>95 (65.5)</td>
<td>1878 (61.5)</td>
</tr>
<tr>
<td>≥25</td>
<td>1266 (37.2)</td>
<td>447 (60.0)</td>
<td>340 (35.1)</td>
<td>50 (34.5)</td>
<td>1170 (38.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>11 (0.3)</td>
<td>9 (1.2)</td>
<td>16 (1.6)</td>
<td>...</td>
<td>6 (0.2)</td>
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<tr>
<td>Diabetes mellitus</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3269 (96.0)</td>
<td>615 (82.5)</td>
<td>935 (96.4)</td>
<td>142 (97.9)</td>
<td>2920 (95.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>137 (4.0)</td>
<td>130 (17.4)</td>
<td>35 (3.6)</td>
<td>3 (2.1)</td>
<td>134 (4.4)</td>
</tr>
</tbody>
</table>

Values are number (percent).
TABLE 2. Distribution of Cases of Selected Neoplasms and Controls According to Presence of Treated Hypertension With Corresponding ORs, as RR Estimators, and 95% CIs (Milan, Italy, 1983–1996)

<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>Treated Hypertension</th>
<th>OR (95% CI)*</th>
<th>OR (95% CI), Treated Hypertension†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>2767 (81.2) 639 (18.8)</td>
<td>1.19 (1.04–1.37)</td>
<td>1.23 (1.08–1.42)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>504 (67.7) 241 (32.3)</td>
<td>1.71 (1.41–2.07)</td>
<td>1.59 (1.30–1.94)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>828 (85.4) 142 (14.6)</td>
<td>0.87 (0.70–1.08)</td>
<td>0.91 (0.73–1.15)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>129 (89.9) 16 (11.0)</td>
<td>0.97 (0.55–1.71)</td>
<td>0.99 (0.56–1.75)</td>
</tr>
<tr>
<td>Controls</td>
<td>2543 (83.3) 511 (16.7)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Treated hypertension values are number (percent).
*Estimates from multiple logistic regression models including terms for age, area of residence, and education.
†Estimates from multiple logistic regression equations including terms for age, area of residence, education, smoking, alcohol intake, parity, menopausal status, and BMI.

Data Analysis

ORs and the corresponding 95% CIs in relation to history of treated hypertension, age at first diagnosis, and time since diagnosis of hypertension were derived from unconditional multiple logistic regression, fitted by the method of maximum likelihood. To allow for possible confounding, all the regression equations included terms for area of residence, age (in quinquenniums), education, smoking habits, alcohol consumption, education, smoking, alcohol intake, parity, menopausal status, and BMI (<20; 20 to 24; 25 to 29; ≥30 kg/m²).

The potential modifying effect of selected covariates was evaluated by comparing the increase in the −2 log likelihood between the models with and without interaction terms with the χ² distribution, with degrees of freedom given by the number of interaction terms.

Results

The distribution of cases of the neoplasms considered and controls according to age and selected covariates is given in Table 1. Patients with endometrial cancer were more frequently older, postmenopausal, and overweight than controls. Thyroid cancer patients were younger, and hence more frequently premenopausal, and more educated.

Table 2 gives the distribution of cases of the 4 neoplasms and the comparison group according to hypertension. The corresponding multivariate ORs were 1.2 (95% CI, 1.1 to 1.4) for breast cancer and 1.6 (95% CI, 1.3 to 1.9) for endometrial cancer. No significant association was observed for ovarian (OR=0.9; 95% CI, 0.7 to 1.2) and thyroid (OR=1.0; 95% CI, 0.6 to 1.8) cancer.

Table 3 shows the relation between age at first diagnosis of hypertension and time since diagnosis for breast and endometrial cancer. No appreciable differences were found according to age at the first diagnosis of hypertension. With reference to time since diagnosis, the ORs for duration of hypertension <5 years were 1.1 (95% CI, 0.9 to 1.4) for breast cancer and 1.5 (95% CI, 1.2 to 2.0) for endometrial cancer. Corresponding values for duration of hypertension >5 years were 1.3 (95% CI, 1.1 to 1.6) for breast cancer and 1.7 (95% CI, 1.3 to 2.1) for endometrial cancer. The trends in risk were significant for both neoplasms.

To address the issue of effect modification, Table 4 considers the relation between hypertension, breast cancer, and endometrial cancer in strata of age at cancer diagnosis and other selected covariates. For breast cancer, the association was stronger at age 55 and over, and consequently in postmenopausal women, and in alcohol drinkers. No appreciable effect modification was evident for education, smoking, and parity (data not shown). The association between treated hypertension and breast cancer risk was significantly stronger in overweight women, with an OR of 1.1 in women with BMI <25 kg/m² and 1.4 in those with BMI ≥25 kg/m² (χ² for heterogeneity obtained from the logistic model=4.689; 1 df; P=0.03). Likewise, the association between hypertension and breast cancer tended to be stronger in subjects with diabetes mellitus, although the interaction term was not significant (OR=1.7; χ² for heterogeneity=2.877; 1 df; P=0.099).

No significant effect modification of any of the covariates considered was observed for endometrial cancer.

To investigate further the combined effect of BMI and hypertension on endometrial and postmenopausal breast cancer, the joint ORs of hypertension and BMI are presented in Table 5.
In normotensive women, there was no trend in OR with increasing BMI with respect to breast cancer, but a marked trend with respect to endometrial cancer was observed. Compared with women who did not report hypertension and had a BMI $<25$ kg/m$^2$, the OR of postmenopausal breast cancer was 1.0 in obese (BMI $\geq 30$) normotensive women but rose to 1.5 (95% CI, 1.1 to 2.0) in hypertensive and obese women. Corresponding ORs for all endometrial cancers were 2.9 (95% CI, 2.1 to 3.8) and 4.9 (95% CI, 3.4 to 6.9).

**Discussion**

The findings of the present study confirm that treated hypertension is associated with endometrial cancer risk. A significant but moderate association was also observed for breast cancer in postmenopausal women, whereas no relation was found for ovarian and thyroid cancer. For endometrial and breast cancer, the risk persisted 5 years since diagnosis. The strength of the association was consistent across strata of several covariates considered for breast and endometrial

### TABLE 3. Distribution of 3406 Cases of Breast Cancer and 745 Cases of Endometrial Cancer and 3054 Controls According to Age at Diagnosis of Treated Hypertension and Time Since Diagnosis With Corresponding ORs, as RR Estimators, and 95% CIs (Milan, Italy, 1983–1996)

<table>
<thead>
<tr>
<th>Time Factor</th>
<th>Breast Cancer</th>
<th>Endometrial Cancer</th>
<th>Controls</th>
<th>OR (95% CI)* for Treated Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypertension</td>
<td>2767 (81.2)</td>
<td>504 (67.7)</td>
<td>2543 (83.3)</td>
<td>1†</td>
</tr>
<tr>
<td>Age at diagnosis of hypertension, y</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>368 (10.8)</td>
<td>115 (15.4)</td>
<td>297 (9.7)</td>
<td>1.21 (1.03–1.44) 1.55 (1.20–2.01)</td>
</tr>
<tr>
<td>$\geq$55</td>
<td>271 (8.0)</td>
<td>126 (16.9)</td>
<td>214 (7.0)</td>
<td>1.25 (1.02–1.54) 1.63 (1.24–2.13)</td>
</tr>
<tr>
<td>Time since diagnosis, y</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>300 (8.8)</td>
<td>109 (14.6)</td>
<td>257 (8.4)</td>
<td>1.12 (0.93–1.35) 1.52 (1.17–1.98)</td>
</tr>
<tr>
<td>$\geq$5</td>
<td>339 (10.0)</td>
<td>132 (17.7)</td>
<td>254 (8.3)</td>
<td>1.34 (1.12–1.61) 1.65 (1.28–2.13)</td>
</tr>
</tbody>
</table>

Distribution values are number (percent).

*Estimates from multiple logistic regression models, including terms for age, area of residence, education, smoking, alcohol intake, parity, menopausal status, and BMI.
†Reference category.

### TABLE 4. Relation of Treated Hypertension to Breast and Endometrial Cancer in Separate Strata of Selected Covariates With Corresponding ORs, as RR Estimators, and 95% CIs (Milan, Italy, 1983–1996)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Breast (Yes: No)</th>
<th>Endometrium (Yes: No)</th>
<th>Controls (Yes: No)</th>
<th>OR (95% CI)* for Treated Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>161:1665</td>
<td>30:155</td>
<td>150:1477</td>
<td>1.05 (0.83–1.33) 1.80 (1.16–2.80)</td>
</tr>
<tr>
<td>55–64</td>
<td>235:714</td>
<td>104:200</td>
<td>168:669</td>
<td>1.38 (1.09–1.73) 2.10 (1.55–2.84)</td>
</tr>
<tr>
<td>$\geq$65</td>
<td>243:388</td>
<td>107:149</td>
<td>193:397</td>
<td>1.34 (1.05–1.70) 1.55 (1.14–2.12)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinkers</td>
<td>194:812</td>
<td>90:155</td>
<td>224:936</td>
<td>0.94 (0.75–1.18) 1.56 (1.13–2.16)</td>
</tr>
<tr>
<td>&lt;2 drinks/d</td>
<td>200:882</td>
<td>68:156</td>
<td>149:775</td>
<td>1.31 (1.02–1.70) 1.75 (1.22–2.51)</td>
</tr>
<tr>
<td>$\geq$2 drinks/d</td>
<td>245:1073</td>
<td>83:193</td>
<td>138:832</td>
<td>1.45 (1.15–1.84) 1.91 (1.38–2.67)</td>
</tr>
<tr>
<td>Menopausal status</td>
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</tr>
<tr>
<td>Pre-perimenopausal</td>
<td>73:1148</td>
<td>15:99</td>
<td>65:959</td>
<td>0.98 (0.69–1.41) 1.78 (0.93–3.42)</td>
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<td>Postmenopause</td>
<td>565:1619</td>
<td>226:405</td>
<td>445:1584</td>
<td>1.30 (1.12–1.51) 1.79 (1.46–2.20)</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>279:1850</td>
<td>67:222</td>
<td>242:1636</td>
<td>1.06 (0.87–1.28) 1.53 (1.11–2.11)</td>
</tr>
<tr>
<td>$\geq$25</td>
<td>357:909</td>
<td>172:275</td>
<td>269:901</td>
<td>1.41 (1.16–1.71) 1.68 (1.31–2.17)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td></td>
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</tr>
<tr>
<td>No</td>
<td>571:2698</td>
<td>176:439</td>
<td>462:2458</td>
<td>1.19 (1.03–1.38) 1.60 (1.29–1.98)</td>
</tr>
<tr>
<td>Yes</td>
<td>68:69</td>
<td>65:65</td>
<td>49:85</td>
<td>1.69 (1.01–2.84) 1.50 (0.89–2.56)</td>
</tr>
</tbody>
</table>

*Estimates from multiple logistic regression models including terms for age, area of residence, education, smoking, alcohol intake, parity, menopausal status, and BMI, when appropriate.
cancer, but in both cases this relation tended to be stronger in overweight (25 to 29 kg/m²) and obese (≥30 kg/m²) patients. The potential confounding effect of several covariates, including age, area of residence, education, smoking, alcohol consumption, parity, menopausal status, and BMI, was controlled for in the analysis. It is conceivable that some aspects of diet, such as a relative absence of fruits and vegetables, is correlated with both hypertension and the risk of these neoplasms. However, further allowance for these factors was unable to totally account for the association. Likewise, allowance for parity, age at first birth, and age at menarche and menopause, which are recognized risk factors for breast and endometrial cancer, did not appreciably modify any of the risk estimates.

Although information on treated hypertension was not independently validated, the choice of a hospital-based design is optimal to investigate aspects of medical history, because cases and controls were similarly sensitized toward recalling diseases in the past. Moreover, the fact that the association was observed in only 2 of the 4 cancers considered is reassuring regarding generalized recall bias. With reference to selection bias, cases and controls were identified in the major teaching and general hospitals in the greater Milan area, and the participation of cases and controls was almost complete. The proportion of controls with hypertension (17%) is consistent with that of the 1990–1991 Italian National Health Survey, when similar age ranges were considered. Also, there is no reason to assume different recall in relation to age at first treatment for hypertension on the basis of disease status. A limitation of the present study is the absence of information on values of blood pressure, severity of the disease, and treatment for hypertension.

The observation that the ORs were higher in subjects who had been diagnosed with hypertension for a longer time argues against surveillance bias, ie, more careful screening for breast or endometrial neoplasms in the few years around the diagnosis of hypertension. This pattern of risk is also consistent with a duration-risk relation, thus suggesting the existence of a real association between hypertension and the risk of these neoplasms.

Detailed discussion on biological mechanisms underlying the possible influence of treated hypertension and female hormone-related cancers goes beyond the scope of this work. Hamet suggested that hypertension may increase the cancer risk by blocking and subsequently modifying apoptosis, thereby affecting the regulation of cell turnover. Hypertension has also been related to insulin resistance and hence to insulin-like growth factor 1, which has been linked to cell growth and neoplastic progression. Other possible interpretations for breast cancer include the relation between treatment for hypertension and increased secretion of prolactin, a hormone with recognized effect on breast tissue differentiation. Hormonal mechanisms are also possible for breast cancer and primarily for endometrial cancer, because hypertension is related to overweight, which in turn is associated with elevated estrogen levels and availability and consequently with the risk of endometrial and postmenopausal breast cancer.

Acknowledgments

This study was supported by the Italian Association for Cancer Research. Dr Soler was the recipient of a fellowship awarded by the Zambon Group, Spain. The authors thank Judy Baggott, M. Paola Bonifacino, and the G.A. Pfeiffer Memorial Library staff for editorial assistance.

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_Hypertension_. 1999;34:320-325
doi: 10.1161/01.HYP.34.2.320

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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