Cancer Incidence in Hypertensive Patients in North Karelia, Finland

Annamarja Lindgren, Eero Pukkala, Aulikki Nissinen, Vesa Kataja, Irma-Leena Notkola, Jaakko Tuomilehto

Abstract—Cancer incidence of 20 529 hypertensive patients included in the community-based hypertension register of the North Karelia Project was determined. A total of 2511 incident cancer cases were obtained among the patients in record linkage with the nationwide Finnish Cancer Registry during the mean follow-up time of 16 years. The age-adjusted incidence rates per 100 000 person-years were 248.4 for men and 171.7 for women, which correspond to that of the general population in the area. The Cox regression model was used to analyze the effect of hypertension-related variables on cancer incidence. In men, the diastolic blood pressure was associated with an increased cancer risk but only in those who smoked >10 cigarettes per day. The functional diagnosis of hypertension (stage I, hypertension with no end-organ damage; stage II, hypertension with left cardiac hypertrophy; and stage III, hypertension with extracardiac organ damage) was associated with the increased risk significantly in men who used antihypertensive drugs at baseline. In women, the diastolic blood pressure was associated with an increased cancer risk in those who did not use antihypertensive drugs at baseline. The functional diagnosis of hypertension was associated with an increased risk only in those who smoked >10 cigarettes per day, but the number of women and cancer cases in this group was small. These results indicate a complex pattern of diastolic blood pressure, functional diagnosis, use of antihypertensive drugs, smoking, and gender in the cancer risk of hypertensive patients. **(*Hypertension*. 2001;37:1251-1255.)**

Key Words: blood pressure ■ cancer ■ antihypertensive agents ■ functional diagnosis ■ incidence ■ record linkage, medical

Over 2 decades ago, in 1975, Dyer et al[1] reported a positive association between high blood pressure and cancer mortality in a cohort of 1233 Chicago Gas Company male employees. The relative risk was 3-fold if the systolic blood pressure (SBP) was >160 mm Hg and 2-fold if the diastolic blood pressure (DBP) was >95 mm Hg, adjusted for smoking, cholesterol, and age, and it could not be explained by the use of antihypertensive drugs. After that study, the relationship between hypertension and cancer has been examined in many cohort studies,[2–13] with varying methodology and magnitude, but the results remain controversial. In many of these studies that measured cancer mortality, a positive association between high blood pressure and subsequent all-site cancer mortality could be observed,[2–5,10,11,13] whereas in 2 studies, the association was inverse in the elderly population.[8,9] The few cohort studies that examined the cancer incidence also gave inconsistent results.[6,7,12] Some studies have also shown that the use of some types of antihypertensive drugs, particularly calcium channel blockers, might be associated with increased risk of cancer,[14,15] but the issue remains unproven.[16,17] The aim of this study was to describe the cancer incidence of hypertensive patients from North Karelia, Finland, and to investigate how the severity of hypertension affects the cancer incidence. This was done by record linkage of the community-based hypertension register of the North Karelia project and the cancer incidence data of the Finnish Cancer Registry.

Methods

The study cohort consisted of 20 886 hypertensive patients who were included in the community-based hypertension register of the North Karelia project. The details of the register are described elsewhere.[18] The register was run within the primary healthcare system in North Karelia province in 1972 to 1988 as part of the North Karelia Project.[19] All subjects who either were on antihypertensive drug treatment because of earlier diagnosis of hypertension or who had elevated blood pressure in 3 subsequent measurements were eligible to be registered. The blood pressure criteria were as follows: 150 and/or 90 mm Hg (<29 years), 160 and/or 95 mm Hg (30 to 64 years), and 170 and/or 95 mm Hg (>65 years). Blood pressure measurements were performed by local nurses and physicians who had received special training for it. The local physicians, following the common protocol of the hypertension register, completed the hypertension register record forms after medical examination of the patient.

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From the Department of Public Health and General Practice, University of Kuopio (A.L., A.N., I.-L.N.), Finland; Finnish Cancer Registry (E.P.), Helsinki, Finland; Department of Neurology (A.N.) and Department of Oncology (V.K.), Kuopio University Hospital, Finland; and Department of Epidemiology and Health Promotion, National Public Health Institute (J.T.), Helsinki, Finland.

Correspondence to Annamarja Lindgren, Department of Public Health and General Practice, University of Kuopio, PB 1627, 70211 Kuopio, Finland. E-mail Lindgren@hytti.uku.fi.

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TABLE 1. The Quartiles of SBP and DBP for Men and Women Among Hypertensive Patients of North Karelia, Finland, in 1972–1996

	Men	Women
SBP		
1st quartile	<151 mm Hg	<156 mm Hg
2nd quartile	151–164 mm Hg	156–170 mm Hg
3rd quartile	165–180 mm Hg	171–190 mm Hg
4th quartile	>180 mm Hg	>190 mm Hg
DBP		
1st quartile	<95 mm Hg	<91 mm Hg
2nd quartile	95–100 mm Hg	91–100 mm Hg
3rd quartile	100–110 mm Hg	101–110 mm Hg
4th quartile	>110 mm Hg	>110 mm Hg

The functional diagnosis of hypertension was based on World Health Organization (WHO) recommendations.[20] Stage I denoted elevated blood pressure without evidence of organic changes in the cardiovascular system. Stage II denoted high blood pressure with left ventricular hypertrophy but without evidence of other organ damage, and stage III denoted high blood pressure with other organ damage attributable to hypertension.

The cohort was linked with the Population Register of Finland to check the validity of the personal identification numbers and to obtain the dates of deaths and emigrations. Thirty-six subjects (0.1%) were excluded from the cohort because they could not be identified. All incident cases of cancer were identified through the population-based countrywide Finnish Cancer Registry. This was done automatically using the personal identification number as key. The follow-up started at the date when the patient was included into the hypertension register and ended at death, emigration, or on December 31, 1996, whichever occurred first. Three hundred twenty-one patients with diagnosed cancer before the beginning of the follow-up were excluded. After these patients were excluded, 12 621 women and 7908 men remained in the cohort.

To demonstrate the absolute overall cancer incidence level among the hypertensive patients, the age-adjusted incidence rates were calculated using the world population age standard.[21] The Cox regression model was used to analyze the independent effects of blood pressure and functional diagnosis of hypertension on the cancer incidence within the cohort. In this analysis, the end point was the person's first diagnosis of cancer. Survival times were censored at death for those who died without cancer during the follow-up. DBP and SBP were analyzed as quartiles (Table 1). Functional diagnosis was coded in 3 stages. Antihypertensive drug treatment indicated a use of any blood pressure–lowering drug at least 5 times a week during the preceding 3 weeks. Other variables used in the analysis were gender, age (as a continuous variable), smoking in 3 categories (nonsmokers, 1 to 10 cigarettes a day, and >10 cigarettes a day), body mass index quartiles (the cutoff points for men were 24, 27, and 29 kg/m^2, and the cutoff points for women were 25, 28, and 32 kg/m^2) and time of registration (1972 to 1976 and 1977 to 1988). All variables were recorded in the beginning of the follow-up and thus present the baseline situation. The variables were first analyzed 1 at a time, adjusting only for age; a multivariate model was then developed using a backward stepwise method. The significance level 0.05 (likelihood ratio method) was used for exclusion of variables. Because possible effects of antihypertensive drugs on the risk of cancer have been widely discussed and because the reported relative risks of cancer associated with hypertension have varied according to the smoking status in earlier studies,[11,12,13] the following interaction terms were also included in the initial multivariate model: smoking category *SBP, smoking category *DBP, smoking category *functional diagnosis, use of antihypertensive drugs *SBP, use of antihypertensive drugs *DBP, and use of antihypertensive drugs *functional diagnosis.

Results

The mean age of hypertensive women at the beginning of the follow-up was 58 years (standard deviation 12 years) and 51 years (standard deviation 13 years) for men. Of the patients, 69% had antihypertensive drug treatment at the time of registration and 31% received nonpharmacological treatment alone or were untreated. A total of 77% of the patients reported that they had been aware of their hypertension at least for 1 year before the registration. The mean time of having been aware of hypertension was 2.3 years in those who did not use antihypertensive drugs and 6.4 years in those with antihypertensive drugs at baseline. In the group with no drug treatment, the proportions of functional diagnosis stages I, II, and III were 75%, 15%, and 10%, respectively. For those receiving drug treatment, the respective proportions were 56%, 21%, and 23%.

The mean length of follow-up for a person was 16 years (standard deviation 7 years). A total of 2511 patients (12% of the cohort) were diagnosed with cancer during the follow-up. The age-adjusted incidence rate per 100 000 person-years was 248.4 for men and 171.7 for women.

Table 2 shows the relative hazards for cancer of selected variables adjusted for age but not for other factors. Smoking was a significant predictor of cancer risk in men, but in women, only smoking 10 or more cigarettes per day was associated with increased risk. The trend associated with body mass index was different in men and women; in women, the highest quartile carried the highest risk, whereas in men, the risk was highest in the lowest quartile of body mass index. The highest quartile of DBP was associated with a significantly increased risk of cancer in both genders, whereas the trend with SBP was less consistent. The risk increased significantly with the increasing stage of functional diagnosis in men but not in women. The use of antihypertensive drugs was not associated with increased risk in either gender.

The building of the multivariate model proceeded in the backward stepwise fashion. All the variables in Table 1, age, time of registration, and all the interaction terms mentioned above, were included in the model at the first step for both men and women.

In men, the variables remaining in the model after stepwise exclusion of nonsignificant parameters were age ($P<0.00005$), smoking ($P=0.006$), interaction of functional diagnosis with use of antihypertensive drugs ($P=0.0006$), and interaction of smoking with DBP ($P=0.002$). In Table 3, this model is shown after the hazard ratios had been calculated to all subcategories of interaction terms compared with only 1 reference category. In the interaction of antihypertensive drugs and functional diagnosis, the reference was the category "no drugs and stage I functional diagnosis"; in the interaction of smoking and DBP, it was the "first quartile of DBP and nonsmoker." The functional diagnosis of hypertension was clearly associated with an increased cancer risk in the group with antihypertensive drugs at baseline but not in those without drugs. In nonsmoker men, there was no association between DBP and cancer risk; in those who smoked >10 cigarettes per day, the cancer risk increased with increasing DBP; and in the group who smoked 1 to 10 cigarettes per day, the association was intermittent.

In women, age ($P<0.00005$), use of antihypertensive drugs ($P=0.005$), DBP ($P=0.009$), body mass index ($P=0.001$), interaction of DBP with use of antihypertensive drugs ($P=0.02$),

TABLE 2. Age-Adjusted Hazard Ratios With 95% Confidence Intervals of Selected Variables in Men and in Women and Number of Cancer Cases in Each Category Among Hypertensive Patients in North Karelia, Finland, in 1972–1996

	Men			Women		
Variable	N	HR	95% CI	N	HR	95% CI
Use of antihypertensive drugs						
No	413	1		345	1	
Yes	597	0.99	0.87–1.13	1152	1.05	0.92–1.18
Functional diagnosis						
Stage I	546	1		854	1	
Stage II	201	1.20	1.02–1.42	330	0.99	0.87–1.13
Stage III	234	1.34	1.14–1.57	281	1.11	0.96–1.27
SBP						
1st quartile	230	1		332	1	
2nd quartile	209	1.02	0.85–1.24	386	0.97	0.84–1.13
3rd quartile	307	1.10	0.93–1.31	432	1.04	0.90–1.20
4th quartile	265	1.15	0.96–1.38	349	1.02	0.88–1.19
DBP						
1st quartile	264	1		387	1	
2nd quartile	307	1.15	0.98–1.36	504	1.13	0.99–1.29
3rd quartile	273	1.01	0.85–1.20	377	1.10	0.95–1.27
4th quartile	167	1.26	1.04–1.53	231	1.21	1.03–1.43
Smoking category						
Nonsmoker	608	1		1404	1	
1–10 cigarettes/day	159	1.71	1.44–2.04	49	0.98	0.74–1.31
>10 cigarettes/day	239	2.18	1.86–2.54	21	1.16	1.05–2.50
Body mass index						
1st quartile	271	1		278	1	
2nd quartile	227	0.79	0.66–0.94	358	1.17	1.00–1.37
3rd quartile	236	0.77	0.65–0.92	376	1.17	1.00–1.37
4th quartile	222	0.79	0.66–0.94	417	1.39	1.19–1.61

HR indicates hazard ratios; CI, confidence intervals; and N, number of cancer cases.

and interaction of functional diagnosis with smoking ($P=0.06$) remained in the model (Table 4). As in men, the hazard ratios for variables of interaction terms are expressed to each subcategory of interaction terms with "first quartile of DBP and no drugs" and "stage I and nonsmoker" as reference categories. The risk of cancer increased with increasing DBP in those without drugs at baseline, but in those women who used antihypertensive drugs, the DBP was not associated with cancer risk. The functional diagnosis of hypertension was associated with increased risk of cancer only in women who smoked >10 cigarettes per day.

To minimize the possible bias that results from preclinical cancers that cause hypertension, the subjects who had cancer diagnosed within 2 years from the registration were excluded and the model building was repeated. All the same variables remained in the final model for both men and women, and the hazard ratios were altered only slightly (not shown).

Discussion

We found the overall age-adjusted cancer incidence rates among the hypertensive patients to be similar to those of the general population in Eastern Finland, suggesting that the all-site cancer risk is not elevated in hypertensive patients in general.

In women, it appears that the high DBP was associated with the increased cancer risk, but only in the group who did not use antihypertensive drugs at the baseline. However, we had no information of the medication use later in the follow-up time nor the type of drugs used. It is likely that women in the higher DBP category had started to use antihypertensive drugs during the follow-up time more than those with lower DBP at the baseline. This can result in a bias, but its magnitude is probably small.

There are some studies associating the use of various types of antihypertensive drugs, mainly calcium channel blockers,[14,15] with the increased risk of cancer, but there are also many studies failing to confirm this association.[16,17] On the other hand, in most of the cohort studies showing an association between elevated blood pressure and increased risk of cancer,[1–6,10–13] the association was independent from the effect of antihypertensive drugs. One study, however, failed to show any association between blood pressure and cancer,[7] and 2 studies found an opposite trend in the elderly population.[8,9] However, it is difficult to distinguish between the effects of hypertension per se and those

TABLE 3. Cox Regression Model in Men With Hazard Ratios and 95% Confidence Intervals and Number of Cancer Cases in Each Category Among Hypertensive Patients in North Karelia, Finland, in 1972–1996

Variable	N	HR	95% CI
Age, y	975	1.08	1.08–1.09
Use of antihypertensive drugs * functional diagnosis			
No drugs and stage I	276	1	
No drugs and stage II	64	1.00	0.76–1.32
No drugs and stage III	50	1.12	0.83–1.53
Drugs and stage I	266	0.92	0.78–1.10
Drugs and stage II	136	1.23	0.99–1.52
Drugs and stage III	183	1.37	1.13–1.67
DBP * smoking category			
Nonsmoker and 1st quartile of DBP	179	1	
Nonsmoker and 2nd quartile	180	1.08	0.87–1.33
Nonsmoker and 3rd quartile	150	0.94	0.75–1.17
Nonsmoker and 4th quartile	85	1.04	0.80–1.35
1–10 cigarettes/day and 1st quartile	33	1.22	0.84–1.77
1–10 cigarettes/day and 2nd quartile	48	2.41	1.75–3.33
1–10 cigarettes/day and 3rd quartile	39	1.35	0.95–1.91
1–10 cigarettes/day and 4th quartile	33	2.61	1.80–3.80
>10 cigarettes/day and 1st quartile	44	1.85	1.33–2.58
>10 cigarettes/day and 2nd quartile	63	2.01	1.50–2.70
>10 cigarettes/day and 3rd quartile	76	2.37	1.79–3.13
>10 cigarettes/day and 4th quartile	45	2.76	1.98–3.86

Abbreviations are as Table 2.

TABLE 4. Cox Regression Model in Women With Hazard Ratios and 95% Confidence Intervals and Number of Cancer Cases in Each Category Among Hypertensive Patients in North Karelia, Finland, in 1972–1996

Variable	N	HR	95% CI
Age, y	1373	1.05	1.04–1.05
Body mass index			
1st quartile	266	1	
2nd quartile	345	1.17	1.00–1.37
3rd quartile	366	1.18	1.01–1.38
4th quartile	396	1.37	1.17–1.60
Use of antihypertensive drugs * DBP			
No drugs and 1st quartile of DBP	27	1	
No drugs and 2nd quartile	91	1.59	1.03–2.44
No drugs and 3rd quartile	124	1.93	1.27–2.93
No drugs and 4th quartile	70	2.00	1.28–3.12
Drugs and 1st quartile	313	1.75	1.18–2.59
Drugs and 2nd quartile	369	1.90	1.28–2.81
Drugs and 3rd quartile	230	1.71	1.15–2.55
Drugs and 4th quartile	149	1.91	1.27–2.89
Smoking category * functional diagnosis			
Nonsmoker and stage I	756	1	
Nonsmoker and stage II	306	0.98	0.86–1.12
Nonsmoker and stage III	274	1.07	0.92–1.24
1–10 cigarettes/day and stage I	35	1.09	0.78–1.53
1–10 cigarettes/day and stage II	5	0.67	0.28–1.61
1–10 cigarettes/day and stage III	6	1.05	0.45–2.35
>10 cigarettes/day and stage I	9	1.11	0.58–2.15
>10 cigarettes/day and stage II	5	2.62	1.08–6.31
>10 cigarettes/day and stage III	4	2.64	0.98–7.07

Abbreviations as in Table 2.

of antihypertensive drugs, because the majority of hypertensive patients are treated and the patients with the most severe hypertension receive drug treatment and more drugs with a higher probability than the patients with less severe hypertension. This is also evident in our data in which a significantly higher proportion of initially treated patients had functional diagnosis stage II or stage III than among untreated ones. Thus, there is a possibility of an indication bias in both directions, ie, a part of the reported drug-related increase in cancer risk may be due to hypertension itself and a part of the reported hypertension-related increase may be due to antihypertensive drugs.

In men, there was a clear trend of increasing cancer risk with increasing DBP for men who smoked >10 cigarettes per day, and in nonsmokers, the DBP did not relate with cancer risk. The same phenomenon has been reported by Wannamethee and Shaper[11] who found a positive association between hypertension and cancer mortality only in current smokers in their study of British men. A similar trend was also noted by Peeters et al among women[13]; the hazard ratio for cancer mortality associated with hypertension was higher for current smokers than for never-smokers. The opposite results have been reported from the study of Swedish men among whom the risk ratio of hypertension and cancer incidence was higher for never-smokers than for ex-smokers and current smokers, but the interaction between smoking and blood pressure was not significant.[12]

The criteria for entering subjects into the hypertension register were markedly higher than the values that are considered as cut points for hypertension at the present. Thus, this hypertension register excluded many subjects who now would be considered as hypertensives. Subsequently, the risks reported in this paper are not the risks associated with hypertension as it is defined today.

As far as we know, this is the first cohort study that measured the cancer outcome in relation to functional diagnosis of hypertension. In a recent, small-nested case-control study from China,[22] a nonsignificant tendency of increased cancer risk associated with left cardiac hypertrophy was reported (odds ratio 1.36, $P=0.5$). We found functional diagnosis to be a significant predictor of cancer in men when adjusted for age. In the final model for men, the effect of functional diagnosis differed markedly according to the drug treatment status, as there was a clear trend in the group with antihypertensive drugs at the baseline but not in those without drugs. In women, the effect of functional diagnosis was apparent only for "heavy" smokers (>10 cigarettes a day), but the number of cancer cases in this subcategory analysis in women was very small. It is possible that the association between functional diagnosis and the risk of cancer reflects the effect of the severity of hypertension, but a possibility of some underlying factor, which increases susceptibility to the development of both end-organ damage and cancer, exists.

For both genders, there were differences in cancer risk depending on the antihypertensive drug treatment status at baseline. Apart from the possible direct effect of drugs, these differences between medication groups may reflect the difference in severity of hypertension or the duration of hypertension, because in the group with antihypertensive drugs, the mean self-reported duration of history of hypertension before the registration was significantly longer than in those without drugs. Also, it is possible that there is a more complex interaction pattern between hypertension, antihypertensive drugs, and other risk factors for cancer.

The cancer registration system in Finland is virtually complete,[23] and the computerized record linkage procedure is precise.[24] Therefore, technical incompleteness did not cause bias in the results. However, there are possible confounding factors that we could not control for in the present study, these include alcohol use, physical activity, and nutritional factors. Also, even though our cohort was larger than in any of the previous studies, the number of cancer cases in some subcategories remained too small for the exact assessment of risks, especially where the expected risks were small.

In some earlier studies, the detected association between hypertension and cancer might in theory have been due to subclinical cancers causing hypertension, an interpretation favored by Buck and Donner.[6] In our study, the results for the Cox regression analysis remained unchanged when cancer cases that occurred during the first 2 years after the registration for hypertension were excluded. Furthermore, the time of registration seldom represented the beginning of the true onset and awareness of hypertension in these patients. Thus, there is no evidence in our study that cancer would have been the causal factor for hypertension.

Our results only concern total cancer incidence to give a picture of the overall risk of cancer associated with hypertension. Because the causes of different cancers differ significantly, the role of hypertension and associated risk factors in the etiology of cancer need to be assessed separately for specific cancer sites. Such an assessment will be performed in further analysis of our data.

The possible pathophysiological mechanisms behind the association between hypertension and cancer remain under discussion. Pero et al[25] reported in 1976 that human leukocytes from hypertensive patients were more likely to experience DNA damage when exposed to carcinogens than leukocytes from normotensives. Many other possible mechanisms are introduced by Hamet.[26] He pointed out that the molecular basis of neither of these diseases is fully understood, and because both disorders reflect proliferative abnormalities, the possibility of a common pathway exists. These could be related, for example, to abnormalities in the apoptotic functions or shortening of telomeres.

Our results indicate a complex pattern of DBP, functional diagnosis, use of antihypertensive drugs, smoking, and gender in the cancer risk of hypertensive patients. The observed association between functional diagnosis of hypertension and risk of cancer needs to be confirmed in separate in-depth studies.

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