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Hydralazine Use in Relation to Cancers of the Lung, Colon, and Rectum

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Summary. It has been suggested, based on animal experiments and limited human data, that the antihypertensive drug hydralazine might be carcinogenic, and among the sites of concern are the lung and colon.

To assess the possible relationship between the use of hydralazine and lung and colorectal cancers in humans, we compared 1006 cases of lung cancer with 3531 hospital control subjects, and 972 cases of colorectal cancer with 3276 controls. Data were collected by interview in hospitals in the United States and Canada.

Overall, 1.1% of the lung cancer cases, 1.6% of the colorectal cancer cases, and 1.5% of the controls had used hydralazine. Compared with those who had never used hydralazine, the relative risk estimate of lung cancer for those who first took the drug at least 18 months before hospital admission was 1.1 (95% confidence interval 0.4–2.9). The estimate for use for at least 1 year was 1.4 (0.5–3.8) and for use for at least 5 years the estimate was 0.9 (0.2–4.3). The corresponding relative risk estimates for colorectal cancer were 1.2 (0.5–2.5) for any use, 1.7 (0.8–3.7) for use for at least one year, and 2.4 (0.8–6.9) for five or more years of use. Other antihypertensive treatments and risk factors, including cigarette smoking in the analysis of lung cancer, were taken into account in these estimates.

Although the effect of use after long latent intervals could not be evaluated, the results provide no support for the hypothesis that hydralazine use increases the risk of lung cancer. There is also no evidence that hydralazine increases the risk of colorectal cancer, but an effect after extended durations of use cannot be ruled out.

Key words: hydralazine, cancer; lung- colon- colorectal cancers, incidence of cancer

There has been some evidence to suggest that the antihypertensive drug hydralazine might be carcinogenic. In a laboratory study the drug was associated with an increase in the incidence of lung tumours in mice [1]. One of its metabolites is hydrazine [2, 3], which can also cause tumour growth in rats and mice; tumour sites have included the lung, large intestine, liver, kidney, and blood vessels [4, 5]. Until recently there was little in the way of data in man, and the results were equivocal. In an uncontrolled study of 116 patients with malignant hypertension treated with hydralazine [6, 7] a few cases of cancer were observed, including two of the lung, two of the breast, and one of the rectum. Subsequently, in a case-control study of breast cancer based on a mammography screening programme, the relative risk estimate for hydralazine used for at least 5 years was moderately elevated, but the increase was not statistically significant [8]. A prospective study of numerous drugs and all cancers conducted by Friedman and Ury identified no statistically significant association with hydralazine use [9], but there were only 409 users, and the power of the study was thus quite limited.

Because of concern about the carcinogenic potential of hydralazine, we have been conducting case-control studies of breast, lung, and colorectal cancers. In 1987 we reported the results for breast cancer, which suggested that overall, hydralazine does not increase the risk [10], although long latent intervals could not be evaluated. Here we report on

the relation of hydralazine use to the risk of lung and colorectal cancers.

Materials, Methods, and Subjects Studied

The methods were similar to those used in our study of breast cancer [10]. Nurse monitors stationed in hospitals in Boston, New York, Philadelphia, Baltimore, Kansas City, Tucson, San Francisco, and London, Ontario, identified patients with various cancers and patients with a wide range of other disorders, who served as potential control subjects. A standard interview was conducted for all subjects. The information obtained included personal characteristics, medical history, and lifetime history of drug use. To elicit drug histories questions were asked about indications for use; information on hydralazine and other antihypertensive and diuretic drugs was obtained by asking about the use of drugs for heart conditions, angina pectoris, high blood pressure, and fluid retention. Details of the duration and timing of use of each drug were obtained. After the patients had been discharged, details of their medical condition, including the primary diagnosis leading to the current hospital admission, were abstracted from the hospital records.

This report is based on interviews conducted from January 1977 to December 1986. Of the patients approached, 4% refused to be interviewed. Most of the subjects (93% of cases and 87% of controls) were interviewed in Boston, New York, Philadelphia, and Baltimore.

Cases

Lung Cancer. Interviewed patients were eligible as cases if they were aged 40-69 years, with a diagnosis of lung cancer made within the six months before hospital admission, and with no other history of cancer. There were 1006 cases, with a median age of 58 years; 603 (60%) were men, 736 (73%) were current cigarette smokers (smoked within the past year), and 230 (23%) were ex-smokers.

Colorectal Cancer. The cases were all patients with a diagnosis of cancer of the colon or rectum made within six months of the current hospital admission. Further requirements were that the patients be aged 40-69 years and have no other history of cancer. There were 972 cases, of whom 46% were men; the median age was 60 years. The distribution of diagnoses included 583 (60%) with colon cancer and 389 (40%) with rectal cancer.

Table 1. Hydralazine use among 1006 cases of lung cancer and 3531 controls

Hydralazine use	Cases		Controls		Stratified relative risk estimate[a] (95% confidence interval)	Multivariate relative risk estimate[b] (95% confidence interval)
	no.	%	no.	%		
Never	995	(98.9)	3479	(98.5)	1.0[c]	1.0[c]
Ist used ≥ 18 m before admission	10	(1.0)	36	(1.0)	0.8 (0.4-1.7)	1.1 (0.4-2.9)
Ist used < 18 m before admission	1	(0.1)	16	(0.5)	--	--

[a] Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] The following factors were included in the multiple logistic model: age, sex, race, religion, marital status, years of education, alcohol consumption, cigarette smoking, history of untreated hypertension, use of diuretics, use of antihypertensive drugs other than hydralazine, geographic area, lifetime number of hospital visits, and year of interview. [c] Reference category.

Controls

Interviewed patients were eligible as controls if they were aged 40-69 years, with primary diagnoses which were judged to be unrelated to antihypertensive drug use, and with no history of cancer.

Lung Cancer. A further exclusion for the analysis of lung cancer was patients with conditions that could be due to undiagnosed lung cancer (e.g. pneumonia). This left 3531 controls, with a median age of 51 years; 1192 (34%) were men, 1421 (40%) were current cigarette smokers, and 886 (25%) were ex-smokers. A total of 1225 controls (35%) were admitted for trauma, 1121 (32%) for acute infections, and 1185 (34%) for various other conditions (e.g. inguinal hernia, diverticular disease). Rates of ever-use of hydralazine were 1.6%, 1.6%, and 1.3% respectively in the three diagnostic categories.

Colorectal Cancer. In the analysis of colorectal cancer, patients with conditions that could be due to undiagnosed colorectal cancer (e.g. bowel obstruction) were not eligible for inclusion. This left 3276 controls, of whom 35% were men; the median age was 50 years. The distribution of diagnoses among the controls was 1225 (37%) with trauma, 1019 (31%) with acute infections, and 1032 (32%) with other conditions (e.g. inguinal hernia, pneumothorax). Rates of ever-use of hydralazine in the three groups were 1.6%, 1.7%, and 1.2% respectively.

Data Analysis

Relative risks were estimated for various categories of hydralazine use, compared with never-use. Because of the possibility that recently initiated use might have begun after the onset of either cancer, the main focus in the analysis was on use that began at least 18 months before hospital admission, that is at least 1 year before the earliest diagnosis.

Relative risk estimates were aggregated across strata of age (decades) and sex by the Mantel-Haenszel procedure [11]. Confidence limits for these stratified estimates were computed by Miettinen's method [12]. To control possible confounding by several factors simultaneously, multiple logistic regression was used [13]. Indicator terms for various categories of hydralazine use were included in the logistic models, along with terms for numerous other factors. In the analysis of lung cancer, these included age, sex, race, religion, marital status, years of education, alcohol consumption, cigarette smoking, history of untreated hypertension, use of diuretics, use of antihypertensive drugs other than hydralazine, geographic area, lifetime number of hospital visits, and year of interview. In the analysis of colorectal cancer the factors controlled included age, sex, religion, marital status, years of education, consumption of alcohol, cigarette smoking, history of untreated hypertension, diuretic use, use of antihypertensives other than hydralazine, geographic region, total lifetime hospital visits, and year of interview.

Results

Lung Cancer

Among the 1006 cases, 11 had used hydralazine (1.1%), compared with 52 of the 3531 controls (1.5%). The stratified relative risk estimate for those who first took hydralazine at least 18 months before admission, compared with those who never took the drug, was 0.8 (95% confidence interval 0.4-1.7) (Table 1); the corresponding multivariate estimate was 1.1 (0.4-2.9). Only one case and 16 controls first took hydralazine within 18 months of admission; these subjects were not considered further.

Most of the cases and controls who first took hydralazine at least 18 months before admission continued to take the drug during the year before admission: 9 of the 10 cases (90%), and 22 of the 36 controls (61%). Timing of use was not analyzed further.

Table 2. Duration of hydralazine use among lung cancer cases and controls

Duration of hydralazine use (years)	No. of cases	No. of controls	Stratified relative risk estimate[a] (95% confidence interval)	Multivariate relative risk estimate[b] (95% confidence interval)
Never	995	3479	1.0[c]	1.0[c]
<1	0	5	--	--
1-4	5	19	1.1 (0.4-3.0)	1.9 (0.5-6.8)
≥5	5	9	1.0 (0.3-3.7)	0.9 (0.2-4.3)
Unknown	0	3	--	--

[a] Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] The following factors were included in the multiple logistic model: age, sex, race, religion, marital status, years of education, alcohol consumption, cigarette smoking, history of untreated hypertension, use of diuretics, use of antihypertensive drugs other than hydralazine, geographic area, lifetime number of hospital visits, and year of interview. [c] Reference category

Table 3. Hydralazine use among lung cancer cases and controls according to various factors

Factor	No. of cases	No. of controls	Stratified relative risk estimate (95% confidence interval)[a]
Age (years)			
40-49	2	12	--
50-59	2	10	--
60-69	6	14	0.8 (0.3-2.3)[b]
Sex			
Male	7	15	0.8 (0.3-2.3)[c]
Female	3	21	0.7 (0.2-2.2)[c]
Cigarette smoking			
Never-smoked	0	14	--
Ex-smoker	4	10	1.0 (0.3-3.6)
Current smoker	6	12	0.9 (0.3-2.5)
Other antihypertensives or diuretics			
Yes	9	36	0.8 (0.4-1.7)
No	1	0	--

[a] Relative to never-use of hydralazine. Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] Stratified by sex only. [c] Stratified by age only

The cases and controls were divided according to the duration of hydralazine use (Table 2). All of the cases and most of the controls took the drug for at least 1 year. None of the relative risk estimates was significantly greater than 1.0: the multivariate estimate for 1-4 years of use was 1.9 (0.5-6.8), and for at least 5 years of use it was 0.9 (0.2-4.3). For use lasting at least 1 year the multivariate relative risk estimate was 1.4 (0.5-3.8).

The subjects were further divided according to categories of age, sex, cigarette smoking, and use of other antihypertensive drugs or diuretics (Table 3). There were small numbers in most categories, and stratified relative risk estimates are only presented for categories in which there were at least three cases

Table 4. Hydralazine use among 972 cases of colorectal cancer and 3276 controls

Hydralazine use	Cases		Controls		Stratified relative risk estimate[a] (95% confidence interval)	Multivariate relative risk estimate[b] (95% confidence interval)
	no.	%	no.	%		
Never	956	(98.4)	3228	(98.5)	1.0[c]	1.0[c]
Ist used ≥ 18 m before admission	12	(1.2)	34	(1.0)	1.0 (0.5-1.8)	1.2 (0.5-2.5)
Ist used < 18 m before admission	4	(0.4)	14	(0.4)	1.1 (0.3-3.8)	1.0 (0.3-3.5)

[a] Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] The following factors were included in the multiple logistic model: age, sex, religion, marital status, years of education, alcohol consumption, cigarette smoking, history of untreated hypertension, use of diuretics, use of antihypertensive drugs other than hydralazine, geographic area, lifetime number of hospital visits, and year of interview. [c] Reference category

Table 5. Hydralazine use among colorectal cancer cases and controls according to cancer site

Hydralazine use	Cases			Controls
	Transverse/ descending/ sigmoid/ unspecified	Caecum/ ascending	Rectosigmoid/ rectum	
Never	424	150	382	3228
Ist used ≥ 18 m before admission	5	1	6	34
Stratified Relative Risk Estimate[a] (95% Confidence Interval)	0.9 (0.3-2.3)	-	1.1 (0.5-2.7)	1.0[b]

[a] Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] Reference category

and three controls. All of the estimates were close to 1.0, and none was significantly different. The relative risk estimate among users of other antihypertensive drugs or diuretics was 0.8 (0.4-1.7).

Colorectal Cancer

Hydralazine use was reported by 16 (1.6%) of the 972 cases and 48 (1.5%) of the 3276 controls (Table 4). Compared with those who never took hydralazine, the stratified relative risk estimate for those whose use began at least 18 months before hospital admission was 1.0 (95% confidence interval 0.5-1.8). The corresponding multivariate estimate was 1.2 (0.5-2.5). Four cases and 14 controls reported first using hydralazine within 18 months of admission (stratified and multivariate relative risk estimates, 1.1 and 1.0 respectively). In the remainder of this report the latter subjects are not considered further.

Of the 12 cases and 34 controls who used hydralazine at least 18 months before admission, 7 (58%) and 22 (65%) respectively continued drug use during the year before admission. The interval since the most recent hydralazine use ranged from 1 year to 10 years among the remaining five cases and from 18 months to 18 years among the remaining 12 controls. Timing of use was not examined further.

Hydralazine use was examined according to tumour site, classified into three groups: transverse, descending, sigmoid, or unspecified site in the colon; caecum or ascending; and rectosigmoid or rectum (Table 5). The stratified relative risk estimates approximated 1.0 for the first and third groups; there was only one case exposed to hydralazine among those whose tumours involved the caecum or the ascending colon.

Hydralazine use is divided according to duration in Table 6. There were no cases who reported use for less than 1 year or for an unknown duration. The multivariate relative risk estimate for 1-4 years of use was 1.1 (0.3-3.7) and for at least 5 years of use it was 2.4 (0.8-6.9). Combining these two categories the multivariate relative risk estimate was 1.7 (0.8-3.7) for hydralazine use of one or more years duration.

In Table 7 hydralazine use is examined within categories of age, sex, religion, and education. There were small numbers in most categories; stratified relative risk estimates are presented only for those categories with at least three cases and three controls. The estimates ranged from 0.5 to 1.5 and none differed significantly from 1.0.

All the hydralazine users had also taken other antihypertensive drugs or diuretics. Thus, it was not possible to evaluate the effect of hydralazine use in the absence of concurrent use of other drugs taken for the same indication, although the effect of such drugs was controlled in the multivariate analyses. To further control potential confounding, the analysis was restricted to subjects who had used antihypertensive drugs or diuretics. Among these subjects (368 cases and 1087 controls), the stratified relative risk estimate for hydralazine use was 0.9 (0.5-1.8).

Table 6. Duration of hydralazine use among colorectal cancer cases and controls

Duration of hydralazine use (years)	No. of cases	No. of controls	Stratified relative risk estimate[a] (95% confidence interval)	Multivariate relative risk estimate[b] (95% confidence interval)
Never	956	3228	1.0[c]	1.0[c]
<1	0	5	-	-
1-4	4	18	0.8 (0.3-2.2)	1.1 (0.3-3.7)
≥5	8	8	2.1 (0.8-5.2)	2.4 (0.8-6.9)
Unknown	0	3	-	-

[a] Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] The following factors were included in the multiple logistic model: age, sex, religion, marital status, years of education, alcohol consumption, cigarette smoking, history of untreated hypertension, use of diuretics, use of antihypertensive drugs other than hydralazine, geographic area, lifetime number of hospital visits, and year of interview. [c] Reference category

Table 7. Hydralazine use among colorectal cancer cases and controls according to various factors

Factor	No. of cases	No. of controls	Stratified relative risk estimate (95% confidence interval)[a]
Age (years)			
40-49	2	10	-
50-59	4	9	1.3 (0.4-4.0)[b]
60-69	6	15	0.7 (0.3-1.7)[b]
Sex			
Male	4	15	0.7 (0.2-2.1)[c]
Female	8	19	1.2 (0.5-2.6)[c]
Religion			
Jewish	4	6	1.2 (0.4-3.9)
Roman catholic	4	14	0.7 (0.2-2.3)
Other	4	14	1.1 (0.4-3.3)
Years of Education			
≤12	3	18	0.5 (0.2-1.5)
>12	9	16	1.5 (0.7-3.4)

[a] Relative to never use of hydralazine. Sex and decade of age taken into account by the Mantel-Haenszel procedure. [b] Stratified by sex only. [c] Stratified by age only

Discussion and Conclusions

The results of this study provide no evidence of an association between hydralazine use and lung cancer. The data were sufficient to exclude, with 95% statistical confidence, an overall increase in risk of three times or more. For use lasting at least 1 year an increase of the order of four times could be ruled out. For use lasting five or more years, there was no evidence of association, but a four-fold increase in risk could not be excluded. It was not possible to examine the effects of hydralazine use after long latent intervals. There was no evidence of association among subgroups of users categorized according to age, sex, and cigarette smoking, but again the numbers of users were small, and for some categories it was not possible to compute informative relative risk estimates.

With regard to colorectal cancer, a 2.5-fold increase in the risk for ever users of hydralazine could be excluded with 95% confidence. However, for extended durations of use the data were limited. There was no statistically significant evidence of association, although the relative risk estimate for five or more years of hydralazine use was 2.4 and the upper 95% confidence limit was compatible with a sevenfold increase in risk. Again, it was not possible to examine use of extended durations that had ended in the distant past. Relative risk estimates for hydralazine use were close to 1.0 when colorectal cancer cases were grouped according to tumour site. There is some recent evidence suggesting that anal cancer may have a different aetiology from other colorectal cancers, sexual practices playing an important role [14]. For this reason anal cancer was not included in this study. In other subanalyses no increase in risk was evident among hydralazine users within strata of age, sex, religion, or years of education. However, comparisons within these subgroups were based on small numbers, and increases in risk as great as four times could not be ruled out.

We considered the possibility that the results could be explained by bias. The diagnosis of lung or colorectal cancer and admission to hospital is virtually inevitable; thus, it is unlikely that cases who were hydralazine users were enrolled selectively. The control conditions were selected to be unrelated to the use of antihypertensive drugs, and many of the control subjects had acute conditions requiring hospital admission. Information bias is also unlikely: the hypothesis is not widely known, and hydralazine is a drug taken regularly in the US and Canada for a serious condition; thus, its use should be well-remembered. Confounding does not loom large as a problem in the present analyses: the major risk factor for lung cancer is cigarette smoking, and it and other factors were controlled in the multivariate models; a similar procedure was followed for colorectal cancer. In particular, there did not appear to be confounding from concomitant use of related drugs (other antihypertensive drugs and diuretics). Not only were they included in the multivariate analyses, but there was also evidence against an association between hydralazine and both cancers among users of these drugs. We conclude that it is improbable that an association between hydralazine use and either cancer was missed because of bias.

Concern about the carcinogenic potential of hydralazine was initially raised by animal experiments [1, 4, 5] and an uncontrolled human study [6, 7].

However, the weight of the epidemiological evidence to date, including the study of Friedman and Ury [9], our previous report on hydralazine and breast cancer [10], and the present study on lung and colorectal cancers, suggests that hydralazine is not carcinogenic in man. There remain unanswered questions, primarily concerning possible effects after latent intervals and long durations of use, and also concerning less common cancers which have not been the subject of detailed investigations. It would be desirable to obtain information on these questions in future studies, but in the meantime the overall picture that emerges for hydralazine is reassuring.

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