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Multiple Myeloma: Relation to Propoxyphene and Other Drugs, Radiation and Occupation

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A case-control study involving 327 cases of multiple myeloma (MM) did not confirm that propoxyphene use is a predisposing factor. The evidence that any drugs are involved in the aetiology of MM is very weak. There was some suggestive evidence that x-ray therapy and certain occupations were predictors of MM.

In screening medicinal drugs for possible carcinogenic effects, we noted an association between propoxyphene use and subsequent multiple myeloma (MM).[1] Among 17927 people who received the drug between 1969 and 1973, 17 developed MM in follow-up through 1978 and 9.4 were expected (standardized morbidity ratio [SMR] = 1.8, $p<0.05$). This hypothesis seemed well worth pursuing further since little is known about the aetiology of MM and drugs are among the few suspected causes.[2] **Also,** the incidence of MM has increased over the past few decades[2] and propoxyphene has been commonly prescribed during **this** period.[3] We therefore conducted a case-control study drawing upon a much larger group of cases, in an attempt to confirm and further characterize the association.

METHODS

In a 1969–1982 computer file of cancer cases among Kaiser Foundation Health Plan (KFHP) subscribers in Northern California we identified 327 people with MM, subsequently confirmed as follows: 316 (96.6%) had diagnostic evidence based on pathological examination of bone niarrow or other tissue and 11 (3.4%) had other strong evidence such as typical abnormal serum proteins. For each case a control subject was selected from the KFHP membership file of the same year as the caw's year of first hospitalization for MM. Control subjects were matched to the cases by sex, year of birth, date of joining the **KFHP,** area of residence (postal zip code), and, when feasible, race (race matched by chart review). Medical charts were niasked after a reference date, six months before the case's diagnosis of MM, and were abstracted by researchers unaware of **the** case-control status. Test-based confidence intervals were calculated using the Rothman–Boice programs.[4]

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RESULTS AND DISCUSSION

Subjects

At diagnosis the cases were aged 32 to 88 years with a median of 64 years; for controls, the age range was 33 to 87 years with a median ***of*** 63 years. Men made up 58.7% of both the cases and the controls. Most of the subjects were white—74.3% of cases and 72.5% of controls. The duration of KFHP membership prior to the reference date (ie. follow-back time in our records) ranged up to 35 years, witli a rnediari of 16 years for both cases and controls.

Propoxyphene

Overall, propoxyphene use was predictive of MM; 135 (41.3%) of the cases and 110 ***(33.6%)*** of the controls received propoxyphcne at least once before the reference date ($\chi^2 = 4.08$, $0.05>p>0.02$). The matched estimate of relative risk (RR) based on a ratio of 82 case-only discordant pairs to 57 control-only discordant pairs was 1.44 (95% confidence **limits** [CL], 1.03, 2.01). However, the largest case-control difference was in the two-year period just before the reference date (Table 1). This suggested that sonic cases had been given the drug for MM symptoms (eg, **back** pain) before MM **was** diagnosed. When attention was restricted to the period two years or more before the reference date, the RR was 1.17 (95% CL, 0.84, 1.64; ratio of discordant pairs 74/63). Siinilarly, **the** (highly-

TABLE 1 *Numbers of multiple myeloma cases and conlrols who received propoxyphene by two-year intervals before reference date. Subjects were counted in any interval in which they received propoxyphene.*

Years before reference date	No. who received propoxyphrne		Case:conirol ratio
	Cases	Controls	
<2	38	18	2.I
2-<4	34	25	1.4
4-C6	38	23	1.7
6-<8	29	25	I.2
8 <10	21	27	0.8
10 <12	18	22	0.8
12 <14	23	14	1.6
14 <16	17	9	I.9
16 <18	9	12	0.8
18 <20	4	7	0.6
20-<22	2	4	0.5
22-<24	1	0	—

skewed) distribution of number of times propoxyphene was prescribed differed significantly (p=0.05 by the one-tailed Komolgorov–Smirnov (KS) test), but when the two years just before the reference date were ignored, the p value was **0.60.**

Table 1 shows that more cases than controls received propoxyphene between zero and eight years and between 12 and **16** years before the reference date. The reverse was true between eight and **12** and between **16** and **22** years before the reference date. Between **22** and 24 years before the reference date, only one case arid no controls received propoxyphene. Although one could hypothesize *post hoc* that propoxyphene acts as a promoter ot' MM during the period of up to about eiglit years before diagnosis, it seems likely that the observed relation to duration is explained by both chance variation and the receipt of propoxyphene for pain due to MM in the few years before the diagnosis was made.

Altogether **114** cases and **86** controls were believed to have estimable total durations of propoxyphene use. The mean total duration of use was **90.2** days in cases and **129.1** days in controls. The median duration in both groups was eight days. The distributions did **not** differ significantly (KS test, p = 0.60).

Among the many indications for propoxyphene use noted, tliose for which cases clearly exceeded controls were largely a variety of types of musculoskeletal pain. This is consistent with the clinical course of MM and with the likelihood that many of the cases were having symptoms well before diagnosis.

Other drugs

Based on a few case reports phenytoin (diphenylhydantoin),[5,6] colchicine and sulfinpyrazone,[7] and cytotoxic drugs[8] have been suggested as predisposing factors for MM.[1,9] We have screened tlie first two of these; no association with MM was found. Through **1980,** among **954** phenytoin users there were 1 observed and **0.6** expected cases of MM; among **849** colchicine users there were **1** observed and **1.1** expected cases. With a two-year lag between dispensing and diagnosis there were no cases of MM observed among users of the cytotoxic drugs, cyclophosphamide **(291** users), vincristine **(62** users), procarbazine *(55* users), chlorambucil **(142** users), or fluorouracil **(355** users). In our drug screening through 1978[1,9] a few drugs showed nominally statistically significant associations with subsequent MM. These, with numbers **of** users, observed cases, and expected cases, respectively, were: carisoprodol, **837,** 5, 0.3; dimenhydrinate, **435, 2, 0.2;** methocarbamol, **5453, 7, 2.6;** and secobarbital, **2884, 6, 1.9.** Since carisoprodol and methocarbamol are commonly prescribed for mulsculoskeletal pain, their association could be artifactual due *to* treatment of early symptoms of MM. These drug-MM associations must be regarded as possible chance associations or hypotheses derived from the thousands of drug-cancer combinations screened.

X-radiation

Radiation has been reported as **a** causal factor in MM.[2] Cases had not received significantly more diagnostic x-ray examinations before the reference date than controls (median **14.1** versus **12.8** per person, p = 0.30 by KS test). **For** x-ray at least two years before the reference date the case-control difference was smaller (respective medians, 10.8 and **10.3).**

Eighteen cases and ten controls had received some form of x-ray therapy before the reference date **(17/9** discordant pairs: RR = **1.89, 95% CL = 0.85, 4.18). For** the nine cases and seven controls with number of rads recorded the respective means were **2451** and **2060** rads per person. Although not statistically significant our data are consistent, within wide confidence limits, with MM associated with x-ray therapy, but not with the amount of radiation ordinarily received from diagnostic x-rays.

Occupation

All occupations noted in the medical records were considered. Although cases and controls differed little with respect to broad occupational groupings, there were some notable differences for the **150** individual occupations looked at (Table **2).** Although not statistically significant here, some occupations with excesses among the cases have been linked to MM previously, ie, carpenters (wood-related industries[10–12]), and

TABLE 2 *Occupations with at least four more cases than controls.*

Occupation	No of cases	No of controls
Student+	7	1
Housekeeper	5	1
Longshoreman	15	7
Janitor	14	9
Warehouseman	11	7
Hospital attendant	8	3
Guard*+	6	0
Other crafts	11	6
Carpenter	10	5
Painter	6	2
Other clerk	8	4

* Verified from manual records because of our surprise at having so many students in this age group.

** $p<0.05$ by two-tailed Fisher's exact test.

painters.[13] The other sizable excesses, particularly in longshoremen, janitors, warehousemen, hospital attendants, and guards, may be clues to some MM-inducing exposure. If exposures to hair sprays or cosmetics become suspect, it should be noted that fewer cases than controls were hairdressers (0 versus 4) or barbers (2 versus 6).

CONCLUSIONS

A case-control study involving 327 cases of MM failed to confirm that propoxyphene use is a predisposing factor. An association between its use and the development of MM up to about eight years later could conceivably represent a causal link, but is most likely due to the use of propoxyphene to treat pain due to MM before it was diagnosed. Follow-up of users of certain other drugs, implicated in a few case reports, did not confirm an association with MM, and associations with still other drugs among the 215 screened were very few. Thus, the evidence that medicinal drugs are involved in the aetiology of MM is very weak. X-radiation therapy but not diagnostic x-rays had an appreciable but non-significant association with subsequent MM. Although numbers were small and therefore of limited reliability, there were some intriguing associations of MM with occupation, two of which support previously reported links to wood and paint exposure.

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