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COEFFICIENTS OF RELATIONSHIP BY ISONYMY AMONG SCOTTISH MALES WITH MULTIPLE PRIMARY CANCERS

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SUMMARY

Patients with heritable cancer syndromes often develop multiple primary cancers (mpc) affecting one or more organs or tissues. However, it is less clear whether the presence of mpc in a patient implies that genetic factors have an important role in aetiology. We have investigated this by comparing the surname distributions of 11205 males with mpc on the Scottish Cancer Register, with corresponding distributions in male controls and in males with individual cancers, by calculating coefficients of relationship by isonymy. Our results suggest that although genetic factors may have a role in the aetiology of mpc, particularly if the cancers affect different tissues or organs, their effect is small compared with that of environmental factors.

KEY WORDS Cancer Surnames Genetics Isonymy

INTRODUCTION

Only about 5% of cancer patients have a pronounced genetic component in the aetiology of their malignancies. These patients may be members of families in which a single gene predisposes to malignancy or of families in which cancers of specific types occur without a clear Mendelian pattern (Schneider *et al.*, 1983). Characteristically, in heritable cancer syndromes, there are multicentric foci of origin within affected paired or non-paired organs or combinations of multiple primaries in different organs or tissues (Schottenfeld, 1982). Patients with inherited types of large bowel cancer show a distinct tendency to develop multiple primaries and familial breast cancer patients have a significantly higher frequency of bilaterality than unselected patients (Anderson, 1982). Inbred mouse strains that are highly susceptible to a given tumour also have a high frequency of multiple primaries (Anderson and Williams, 1985).

Subgroups of patients with bilateral or multifocal forms of common neoplasms such as those of breast and colon show much higher familial risks than other patients with these neoplasms. Moertel (1966) compared the occurrence of malignant disease in the first degree relatives of (1) patients with multiple primary malignant neoplasms, (2) patients with a single neoplasm and (3) patients free from malignant disease. The only patients included in group (1) were those with neoplasms of different tissues or organs since it had been suggested that different aetiological mechanisms were involved in multiple primary cancers of the same organ. The occurrence of malignant disease in the three groups of relatives was 9.3%, 7.3% and 7.4% respectively. By contrast Kakizaki *et al.* (1992) found that amongst patients with genitourinary cancer, there was no difference between those

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who had a single cancer and those who in addition had multiple primary cancers of other organs, in the frequency of a positive family history of cancer.

These findings suggest that genetic susceptibility may be an important factor to consider for multiple primary cancer (mpc) patients. Further evidence for this comes from the fact that Li Fraumeni syndrome, a rare autosomal dominant susceptibility to a variety of cancers, is associated with inherited mutations of the tumour suppressor gene p53 (Malkin *et al.*, 1990) and the gene BRCA1 causing susceptibility to early onset breast cancer and ovarian cancer has recently been isolated (Miki *et al.*, 1994). Two genes causing non-polyposis colorectal cancer, endometrial cancer and a number of other cancers have also been identified (Leach *et al.*, 1993; Papadopoulos *et al.*, 1994).

However the occurrence of mpc may be due to the fact that the same aetiological factors are operating in the pathogenesis of several neoplasms. For example, in a study in Connecticut, Curtis *et al.* (1985) found that common environmental exposures seemed responsible for the excess occurrence of many second cancers, particularly those related to cigarette smoking, alcohol consumption or both. In a study of mpc in Denmark, Storm *et al.* (1985) found that for cancers suspected to have a hormone or dietary fat related association, significant reciprocal relationships were seen among cancers of the endometrium, ovary and colon.

Cancer treatment is also probably an important factor in second cancer development. There is experimental and epidemiological evidence of carcinogenic activity of antineoplastic chemotherapy that has been used during the last three decades and neoplasms of many types may be induced by ionising radiation (Schottenfeld, 1982).

In a previous study (Holloway and Sofaer, 1992a) we used the coefficient of relationship by isonymy to investigate the importance of inherited susceptibility to carcinoma of the stomach, colon, rectum, prostate and bladder. In a subsequent investigation (Holloway and Sofaer, 1992b) we reanalysed this data and found that early onset, a characteristic of hereditary cancers, was not associated with greater isonymy suggesting that early age at onset is not widely associated with a familial predisposition to malignancy. In the present study we investigated the importance of genetic factors amongst patients with mpc. Isonymy amongst males with mpc on the Scottish Cancer Register was compared with that found amongst cancer patients in the first study (Holloway and Sofaer, 1992a) and amongst controls.

MATERIALS AND METHODS

Registrations, during the period 1968–87, of males with mpc, were obtained from the Scottish Cancer Register. Surname distributions amongst these males were compared with those amongst all males who were born married or who died in Scotland in 1976 (supplied by the Office of the Registrar General for Scotland). They were also compared with surname distributions amongst males with cancer of the stomach, colon, rectum, prostate and bladder previously investigated (Holloway and Sofaer, 1992a). These males were selected only for the presence of the specified cancer and some may have had other cancers in addition.

Surname distributions were compared using the coefficient of relationship by isonymy, Ri, which can be considered as half the probability that two people selected at random have the same surname. The factor of 1/2 is introduced so that the relationship corresponds with the expected proportion of shared autosomal genes on the assumption

of monophyly of surnames. Values of Ri were calculated within and between groups of cancer cases and controls according to Lasker (1977, 1985) and the significance of the difference between two Ri values was assessed by the method of Fox and Lasker (1983). Further details of the method of calculation are given by Holloway and Sofaer (1992a).

Values of Ri were calculated for mpc cases both for Scotland as a whole and within and between local government regions and compared with values for controls and individual cancers previously calculated (Holloway and Sofaer, 1992a). MPC cases were compared with all controls and also with control deaths only. Control deaths, which accounted for 32% of all controls, had an age distribution more similar to that of the mpc cases. Mean age in 1976 for mpc cases, some of whom died before 1976, was 66 years compared with mean ages of 40 years for all male controls and 67 years for control deaths.

The Wilcoxon Matched Pairs Signed Ranks Test (Siegel, 1956) was used to compare the sets of within and of between region Ri values for mpc with the corresponding sets of values for controls and for the individual cancers. Values for the island regions were not included in these comparisons because the number of cases was small. In expressing statistical significance account was taken of the large number of comparisons by multiplying individual probabilities by the number of comparisons made at each stage.

Because of the suggestion (Moertel, 1966) that different aetiological mechanisms are involved in patients with neoplasms of different tissues or organs, we repeated the calculations after excluding all the mpc cases where all tumours were of the same site (defined as those having the same first 3 digits in the ICD 9 classification (International Classification of Diseases, 1977)).

All calculations were repeated using rare surnames only, considered to be those with an occurrence of less than 1 per 1000 amongst births, marriages and deaths for 1976 in Scotland as a whole (Holloway and Sofaer, 1989).

RESULTS

Numbers of males with mpc in each of the regions of Scotland are given in Table 1. Numbers of control males and males with individual cancers in each region are given by Holloway and Sofaer (1992a). The total number of male controls was 101,836 and the total number of males with the individual cancers ranged from 8,570 to 14,712.

Ri values for males with all surnames

Within region Ri values for mpc cases, controls and individual cancer cases are given in Table 2 for the 9 mainland regions of Scotland and for Scotland as a whole. In none of the 7 comparisons of the 9 within region values for total mpc cases with the corresponding values for controls and individual cancers was the median difference (mpc – other) significantly greater than zero. The same was true when considering only the cases with mpc of different sites.

By contrast some significant differences were found when comparing the between region values. The median difference between the Ri value for all mpc cases and that for all male controls was significantly greater than zero ($p<0.001$) . When considering mpc of different sites only, the median difference from all male controls was significantly greater than zero ($p<0.001$) as also was the median difference from male death controls ($p<0.05$). None of the other differences was significant. A summary of the results of the comparisons of Ri values for mpc cases with those for male controls is given in Table 3.

Table 1. Numbers of males with mpc in each of the regions of Scotland and numbers of cases with cancers of different sites

Region	Total cases	Cases with cancers of different sites
Highland	500	304
Grampian	1479	1188
Tayside	812	711
Fife	844	657
Lothian	2284	1772
Borders	320	233
Central	531	407
Strathclyde	3952	3283
Dumfries and Galloway	293	230
Orkney	60	43
Shetland	50	35
Western Isles	80	53
SCOTLAND	11205	8916

The median differences (mpc-controls) are given in this Table and are also expressed as a percentage of the corresponding median control values. The median control values are given in Table 4.

There were no significant differences between the Ri value for mpc cases in Scotland as a whole and the corresponding values for controls and for individual cancers whether or not total mpc cases or only those with cancers of different sites were considered.

Ri values for males with rare surnames

The calculations were repeated using mpc cases, controls and individual cancer cases with rare surnames only. Rare surnames accounted for 57%, 59% and 56% respectively of mpc cases, controls and individual cancers. The within region values are given in Table 5.

As when considering males with all surnames, the median difference between the Ri values for mpc cases and those for individual cancer cases was not significantly greater than zero in any of the comparisons of within or between region values.

In the comparison of within region values the median difference between the value for all mpc cases and that for all male controls was significantly greater than zero ($p<0.05$) (Table 3). When considering only mpc cases with cancers of different sites the above difference just failed to reach significance . None of the other differences was significant.

Among the comparisons of between region values two of the median differences were significantly greater than zero. These were in the comparisons of all mpc cases ($p<0.05$) and those with cancers of different sites ($p<0.01$) with all male controls (Table 3).

No significant differences were found in the comparisons of Ri values for mpc cases in Scotland as a whole with the corresponding values for controls or individual cancers.

Table 2. Within region Ri values ($x10^5$) for mpc cases, controls and individual cancer cases – all surnames.

Region	Multiple primary cancers		Controls		Individual cancers				
	Total	Different sites	All males	Male deaths	Stomach	Colon	Rectum	Prostate	Bladder
Highland	438.1	407.1	318.3	441.7	534.0	614.6	494.2	651.4	626.5
Grampian	192.4	186.6	167.1	203.3	204.4	185.0	221.0	199.2	198.8
Tayside	132.7	132.9	113.4	114.8	176.0	167.9	155.4	133.2	150.2
Fife	113.7	113.0	104.9	132.5	118.6	153.8	110.5	137.1	139.4
Lothian	105.1	101.8	87.7	98.1	109.7	116.9	101.9	119.2	118.3
Borders	150.9	142.4	132.9	139.8	132.7	192.9	203.9	262.8	100.4
Central	92.4	91.4	106.3	128.7	111.4	119.0	99.8	133.5	95.0
Strathclyde	99.0	100.7	81.1	90.2	104.6	109.0	95.7	104.3	94.6
Dumfries*	104.0	119.6	101.5	105.7	134.4	83.9	106.3	124.5	67.8
SCOTLAND	105.5	105.7	86.6	96.4	109.0	115.1	104.2	114.8	104.6

*Dumfries and Galloway

Table 3. Median differences between Ri values for mpc cases and controls and values expressed as a percentage of the corresponding median control value.

MPC group	Comparison with all male controls		Comparison with male death controls	
	Median difference		Median difference	
	Actual ($x10^5$)	%+	Actual ($x10^5$)	%+
Within regions				
All MPC	18	17	-2	-2
MPC - different sites	18	17	3	2
All MPC - rare surnames	9*	22	0	0
MPC - different sites and rare surnames	11	27	0	0
Between regions				
All MPC	13 ***	14	2	2
MPC - different sites	16 ***	18	7 *	7
All MPC - rare surnames	2 *	9	0	0
MPC - different sites and rare surnames	2 **	9	0	0

* p<0.05, **p<0.01, ***p<0.001
+ percentage of corresponding median control value

Table 4. Median control Ri values ($x10^5$)

		All males	Male deaths
Within regions			
	All surnames	106	129
	Rare surnames	41	55
Between regions			
	All surnames	91	99
	Rare surnames	23	24

DISCUSSION

Within region Ri values for mpc cases were greater than for all male controls but only one of the median differences was significantly greater than zero (Table 3). No differences were however found in the comparisons with male death controls. This finding probably reflects the age difference between the two control groups, the mpc cases being similar in age to the male death controls. In a previous study in which the same control data were analysed (Holloway and Sofaer, 1989), we found that Ri within regions was greatest for deaths and lowest for births and it was felt that this was because deaths

occur predominantly amongst the elderly who are less likely to have immigrated from elsewhere during their lifetime. The effect of this factor on the difference between Ri values would be expected to be greater using rare surnames only. In the present study the median difference between the Ri values of mpc cases and of all male controls reached a maximum of 27% of the median control value using mpc cases with cancers of different sites and rare surnames only.

In all 4 comparisons of the between region values of mpc cases and all male controls the median difference (mpc – controls) was significantly greater than zero (Table 3). Smaller differences were found using rare surnames and this was probably because the number of mpc cases included was reduced and was only greater than 500 for 4 regions. In the study of Holloway and Sofaer (1989) higher between region Ri values were found for deaths than for marriages and births and this was thought to be due to a greater number of individuals per name amongst deaths and the fact that between region values were determined mainly by common names . From the results of the above study it can be calculated that the median difference, using all surnames, between Ri values for male deaths and all for males (all events combined) for the non island regions is $9x10^5$. Thus some of the difference between Ri values for mpc cases and all male controls could be due to this factor. However the observed differences from all male controls were greater than those found in the above study. Taking cancers of different sites only and all surnames, a significant difference was also found using male death controls although the median difference was only 7% of the median control value.

These results suggest that although genetic factors may be involved in the aetiology of mpc in general and be of greater importance for individuals where the cancers affect different sites, the effect of these factors is not great. The lack of any observable difference between within region values for mpc cases and male death controls probably reflects the much greater importance of environmental factors in disease aetiology. In the studies of Curtis *et al.* (1985) and Storm *et al.* (1985) cigarette smoking and alcohol consumption were felt to be responsible for many second tumours. In the former study 25% of the excess second cancers developed at sites strongly linked to the use of tobacco, alcohol consumption or both, notably the buccal cavity, pharynx, oesophagus and respiratory tract. In our study these sites were involved in 18% of first tumours and 31% of second tumours. The above authors also reported associations between second tumour development and dietary factors and treatment of the first cancer.

The small significant differences found when comparing between region values for mpc cases and controls probably reflect small differences in surname distribution between these groups but the statistical methods used are not sensitive enough to detect them when considering a relatively small number of within region Ri values.

Boice *et al.* (1985) felt it unlikely that hereditary cancers contributed substantially to the incidence of second tumours although some complexes of tumours result from genetic factors . Although Moertel (1966) found a greater occurrence of malignant disease in the first degree relatives of mpc cases than in the relatives of patients with single cancers and of controls, the difference between the groups was small and he was cautious about the interpretation of his results in view of the limitations of the study.

Median differences between Ri values for mpc cases and for the individual cancers were not significantly greater than zero. There was actually a tendency for Ri values for the individual cancers to be greater than for mpc cases (Tables 2 and 5). The cases with individual cancers were ascertained because they had one of the 5 cancers but some may

Table 5. Within region Ri values($x10^5$) for mpc cases, controls and individual cancers – rare surnames

Region	Multiple primary cancers		Controls		Individual cancers				
	Total	Different sites	All males	Male deaths	Stomach	Colon	Rectum	Prostate	Bladder
Highland	171.5	179.8	115.9	184.0	147.7	249.0	165.3	301.2	157.4
Grampian	108.3	106.9	74.9	105.9	108.0	106.9	118.6	120.3	123.2
Tayside	50.4	46.7	41.2	46.4	55.8	45.1	53.9	50.8	53.1
Fife	45.6	39.8	41.1	55.6	45.7	72.2	66.5	53.2	42.6
Lothian	28.1	28.8	27.7	33.1	31.6	28.4	31.0	34.8	27.5
Borders	85.7	100.0	66.4	91.4	80.5	124.3	77.4	82.4	51.6
Central	43.4	50.1	38.7	40.8	62.1	39.6	53.6	59.4	40.6
Strathclyde	30.9	31.5	28.7	31.2	33.8	33.1	34.2	31.8	31.5
Dumfries*	77.6	95.2	56.6	55.2	51.3	61.8	69.9	50.6	32.7
SCOTLAND	27.2	27.7	24.6	27.5	27.7	28.9	29.7	29.9	27.5

*Dumfries and Galloway

have had other cancers in addition. However our mpc cases represent only 5.3% of all male cancer registrations in the time period considered so only a few of our individual cancer cases are likely to have had multiple primaries and thus any bias will be small.

Thus our findings suggest that genetic factors may be involved in mpc cases especially if the cancers affect different sites but genetic factors would appear to be much less important than environmental factors and no more important than for the individual cancers considered.

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