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Risk of cancer death in first-degree relatives of patients with hereditary non-polyposis cancer syndrome (Lynch type II): a study of 130 kindreds in the United Kingdom

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To estimate the relative risks of cancer in first-degree relatives of index patients, 130 pedigrees of dominantly inherited Lynch type II cancer family syndrome have been analysed. The risk of death from all causes was significantly increased in women over 45 years of age and the overall liability to cancer in women was greater than for men. A sevenfold increase in risk of colon cancer was found in both sexes. In female relatives the risk of breast cancer was increased fivefold and lifetime risk of breast cancer was 1 in 3·7. A screening programme based on estimated risks could be offered to first-degree relatives of index patients with Lynch type II cancer family syndrome.

Keywords: Hereditary non-polyposis colon cancer, HNPCC, dominant inheritance, relative risks

Family aggregation of colorectal and breast cancer is well recognized by patients and their surgeons and was initially reported by Warthin[1] in 1913. Anderson[2] and Lovett[3] reported an increased risk of colorectal cancer in first-degree relatives of affected men and women, and the risk was particularly high when index patients were young. Anderson[4] and Ottman *et al.*[5] reported an increased risk of breast cancer in first-degree relatives of affected patients that was greater when breast cancer in the index patients was bilateral or affected premenopausal patients. Lovett[3] also reported an increased risk of gastric cancer and breast cancer among first-degree relatives of index patients with colorectal cancer.

Dominant inheritance of a liability to several types of malignancy was reported by Warthin[1] and the importance reinforced by Lynch and Krush[6] in 1971, who revisited Warthin's original family and greatly extended the pedigree. The cancer family syndrome described has been called hereditary non-polyposis colorectal cancer, or Lynch type II syndrome, and extensive kindreds have been reported by Lynch *et al.*[7], usually including colorectal cancers occurring in young adults with a variety of malignancies including breast, pelvic, gastric, skin, brain and bladder. The contribution of hereditary non-polyposis colorectal cancer Lynch type II syndrome to the overall incidence of colon cancer has been estimated as between 6 and 10 per cent by Lynch *et al.*[7], but the risks to relatives of developing specific malignancies has not been estimated.

In Family Cancer Clinics at the Royal Free and St. Mark's Hospitals, London, 999 patients have attended because of their concern about family risks of breast and colorectal cancer. From the pedigrees obtained, those with evidence of dominant inheritance compatible with Lynch type II syndrome have been selected and used to calculate the relative risks of a variety of malignancies, and the lifetime risks have been estimated for first-degree relatives of patients with Lynch type II cancer family syndrome. The findings illustrate the need for surgeons to identify patients belonging to families with a Lynch type II cancer family syndrome and the implications of this diagnosis for the screening of relatives of index patients.

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Patients and methods

From 550 patients who have attended St. Mark's Hospital Family Cancer Clinic because of their concern about the family risks of colon cancer and 449 patients who have attended the Royal Free Hospital Genetic Clinic because of their concern about the family risks of breast cancer, 130 pedigrees have been identified with evidence of dominant inheritance of cancers compatible with the Lynch type II cancer family syndrome. Index patients were family members who developed either colon or breast cancer before the age of 50, and all families exhibited a dominant mode of inheritance of two or more different malignancies within the pedigree. Patients attending the clinic were either referred by general practitioners and hospital consultants or presented themselves because of information received from friends, relatives or the media.

The age and cause of death in relatives was verified, where possible, by reference to hospital records or death certificates. Information about living relatives was checked from hospital records. Standard life table methods[8] were used to estimate the years at risk by decades, contributed by male and female first-degree relatives. Index patients were excluded from life tables. The median year in which deaths were notified was 1975 and the tables from the Office of Population Censuses and Surveys (OPCS)[9] for 1975 were used to calculate the expected number of deaths among first-degree relatives in 10-year age groups from age 15. The Poisson distribution[10] was used to estimate the significance of any difference between the observed and expected number of deaths. Standard errors obtained from the formula $\sqrt{(\text{observed}^2/\text{expected})}$ for small numbers were used to calculate 95 per cent confidence limits of relative risks; confidence limits were obtained from the table in Breslow and Day[11].

The relative risks of death from all causes, death from all cancers, and death from malignancies recognized to be associated with Lynch type II cancer family syndrome were calculated in three age groups (15–44, 45–64, and 65 and over), and where these were increased the actual risk of death from cancer was calculated.

Results

From 999 index patients attending the Family Cancer Clinics at the Royal Free and St. Mark's Hospitals, 130 pedigrees were identified with Lynch type II cancer family syndrome. In all, 99 index patients with breast cancer under the age of 50, and 31 with colon cancer under the age of 50, were identified. Of the first-degree relatives, 885 had reached the age of 15.

Table 1 shows years at risk in three age groups (15–44, 45–64

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and 65 years and over) for both male and female first-degree relatives of index patients with either colon or breast cancer. *Tables 2–5* show the observed number of deaths and relative risks for first-degree relatives for all deaths, all cancers, and cancers of the colon and breast.

Table 2 shows that the expectation of life was diminished in the middle age groups in first-degree relatives of index patients with breast cancers and for the older female relatives of index patients with breast cancer. However, for men, death from all causes was not significantly affected in any age group. *Table 3* shows that there was an increased risk of death from all cancers for both men and women from the age of 45 and that the relative risks for women were between 1·5- and 3·4-fold greater than those for men. *Table 4* shows that both men and women were at increased risk of colon cancer at all ages. *Table 5* shows that the risk of breast cancer was also increased in each age group.

The distribution of risks of death from colon, breast and pelvic cancers was similar for first-degree relatives of index patients with breast or colon cancer. It was therefore decided to combine the experience of the relatives of the two groups in considering the risks of rarer malignancies.

Women were also found to be at increased risk of uterine and ovarian cancers, the risk of ovarian cancer being significantly increased, with a relative risk of 3·18. Both men and women were found to be at increased risk of pancreatic and gastric cancer, but for pancreatic cancer only the results for women were statistically significant. The risks for melanoma were significantly elevated for women, but for men the increase

Table 1 *Years at risk contributed by first-degree relatives of index patients with breast cancer and colon cancer by age groups*

Age group of relatives (years)	Index patients with breast cancer		Index patients with colon cancer	
	Female relatives	Male relatives	Female relatives	Male relatives
15–44	10320	7395	2950	2390
45–64	3825	3075	935	1015
65+	1260	1095	332	360
Total	15405	11565	4217	3765

Table 2 *Observed deaths from all causes and the relative risks in first-degree relatives of index patients with breast and colon cancer*

Age group of relatives (years)	Index patients with breast cancer				Index patients with colon cancer			
	Female relatives		Male relatives		Female relatives		Male relatives	
	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk
15–44	8	1·02	10	1·08	16‡	7·37	3	1·0
45–64	39*	1·51	46	1·21	16‡	2·56	15	1·20
65+	73†	1·42	69	0·89	16	0·80	21	0·83
Total	120‡	1·41	125	1·0	48‡	1·93	39	0·95

Significance of difference from expected: * $P<0·05$, † $P<0·01$, ‡ $P<0·001$ (Poisson distribution)

Table 3 *Observed deaths from all cancers in first-degree relatives of index patients with breast and colon cancer and their relative risks*

Age group of relatives (years)	Index patients with breast cancer				Index patients with colon cancer			
	Female relatives		Male relatives		Female relatives		Male relatives	
	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk
15–44	5	1·82	1	0·62	14‡	18·67	2	3·77
45–64	30‡	2·71	20†	1·83	16‡	5·97	11‡	3·09
65+	44‡	4·51	37‡	2·14	11‡	3·98	6	1·05
Total	79‡	3·44	58‡	1·95	41‡	6·62	19†	1·94

Significance of difference from expected: † $P<0·01$, ‡ $P<0·001$ (Poisson distribution)

Table 4 *Observed deaths from colon cancer and relative risks in first-degree relatives of index patients with breast and colon cancer*

Age group of relatives (years)	Index patients with breast cancer				Index patients with colon cancer			
	Female relatives		Male relatives		Female relatives		Male relatives	
	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk	Deaths	Relative risk
15–44	1	5·55	0	–	5‡	102·04	1	20·8
45–64	5†	4·15	7‡	6·59	4‡	13·75	4‡	11·53
65+	10‡	5·76	13‡	11·92	4†	7·77	1	1·45
Total	16‡	5·14	20‡	6·06	13‡	15·20	6‡	5·55

Significance of difference from expected: † $P<0·01$, ‡ $P<0·001$ (Poisson distribution)

Table 5 *Observed deaths from breast cancer and the relative risks in first-degree relatives of index patients with breast and colon cancer*

Age group of relatives (years)	Relatives of index patients with breast cancer		Relatives of index patients with colon cancer	
	Deaths	Relative risk	Deaths	Relative risk
15–44	2	2·34	2*	8·62
45–64	12†	3·91	3*	4·10
65+	15‡	9·04	4‡	8·71
Total	29‡	5·26	9‡	6·34

Significance of difference from expected: * $P<0·05$, † $P<0·01$, ‡ $P<0·001$ (Poisson distribution)

Table 6 *Living first-degree relatives with cancer by age groups*

Age group of relatives (years)	First degree relatives of all index patients			
	Female		Male	
	Cancer type	*n*	Cancer type	*n*
15–44	Basal cell carcinoma	1	Colon	5
	Melanoma	1		
	Ovary	7 (1 vestigal)		
	Breast	1		
	Colon	2		
45–64	Breast	9	Brain tumour	1
	Breast and ovary	1	Colon	2
	Cervix	3	Skin	1
	Uterus	5	Unspecified	2
	Bladder	1		
65	Breast	10	Bladder	1
	Colon	3	Colon	9
	Melanoma	1	Colon and prostate	1
	Ovary	1	Lung	2
	Sinus	1	Prostate	3
	Uterus	1		
	Basal cell carcinoma	1		
	Skin	1		

was not significant. The risk of lung cancer was increased in women but paradoxically showed a nearly 50 per cent reduction in risk in men. This is consistent with the observations of Lynch *et al.*[7]. The risks of prostate cancer and cancer of lymphatic and haemopoietic tissue were marginally elevated, but the increases were not statistically significant. *Table 6* shows the experience of malignancy in living first-degree relatives by age groups and clearly reflects the increased risk of cancer deaths.

Tables 7 and *8* show a summary of the relative risks and the estimated lifetime risks of death from breast, colon and other malignancies in the first-degree relatives of all index patients in women and in men respectively.

Discussion

Lynch and his co-workers have drawn attention to the increased risk of a variety of malignancies in relatively few large kindreds with cancer family syndrome. In the absence of any diagnostic biomarker it is only from the pedigree that cancer family syndrome can be identified, but the recognition of close relatives of young patients in ordinary surgical practice with colon or breast cancer who may be at high risk of developing a variety of different cancers offers an opportunity for screening a group of people who are anxious and motivated.

Only one first-degree relative under the age of 50 was required to bring patients in our study to the Family Cancer Clinic but two or more relatives affected with a variety of cancers are required to make the diagnosis of Lynch type II syndrome. Since penetration is incomplete, the second cancer in the pedigree is not always in a first-degree relative of the index patient, but dominance can be recognized and the diagnosis can be made if a family history is obtained. Since the analysis was designed to estimate the risks of cancer among first-degree relatives in order to warn surgeons of the need to institute screening programmes for first-degree relatives of young patients with breast and colon cancer, it was decided to include all first-degree relatives of index patients so as to estimate their risks, but to exclude the index patients to overcome ascertainment bias[12].

This analysis of 130 pedigrees allows an estimation of the risks to first-degree relatives of patients with a family history characteristic of Lynch type II syndrome. The risks are relevant not only to a few large kindreds but to a large number of families who recognize an increased liability to cancer among their relatives. *Tables 7* and *8* summarize the findings and show the estimated lifetime risk of death for each type of cancer involved.

There was a notable increase in risk of colon cancer in both sexes which, with melanoma, was disproportionately increased when compared with the overall increase in risk of all cancer deaths and gave a lifetime risk of 1 in 6. For men, the sixfold increase in risk was 1·7 times the expected contribution to all cancer deaths and gave a lifetime risk of 1 in 8. Since most colon cancers arise in a premalignant adenoma, this provides an opportunity for screening and removal of premalignant polyps in an undeniably high-risk group. The fivefold increase in risk of breast cancer in women gave an estimated lifetime risk of 1 in 3·7. Furthermore, the risk was not over by the age of 65 and it may be that screening this high-risk group could successfully reduce mortality as well as morbidity. Cancer of the pancreas and stomach were increased to a lesser extent, and lung cancer

Table 7 *Summary of deaths from cancer in female first-degree relatives of all index patients and all age groups showing observed deaths, relative risks, 95 per cent confidence limits and the lifetime risks*

Cause of death	No. of deaths	Relative risk	95% confidence limits	Lifetime risk
All causes	168*	1·53	1·18–1·61	
All cancers	122*	4·10	3·30–4·71	1 in 1
Colon cancer	29*	7·31	4·70–10·1	1 in 6
Breast cancer	38*	5·18	3·67–7·1	1 in 3·7
Uterine cancer	8†	3·77	1·61–7·37	1 in 40
Ovarian cancer	7†	3·18	0·90–4·66	1 in 20
Pancreatic cancer	7*	5·95	2·32–11·93	1 in 14
Melanoma	4*	10·0	2·71–25·4	1 in 50
Stomach cancer	10*	4·92	2·27–8·68	1 in 14
Lung cancer	6	1·6	0·59–3·49	1 in 17

Significance of difference from expected: * $P<0·001$, † $P<0·01$ (Poisson distribution)

Table 8 *Summary of deaths from cancer in male first-degree relatives of all index patients and all age groups showing observed deaths, relative risks, 95 per cent confidence limits and the lifetime risks*

Cause of death	No. of deaths	Relative risk	95% confidence limits	Lifetime risk
All causes	164*	0·98	0·78–1·1	
All cancers	77*	1·94	1·48–2·34	1 in 1·7
Colon cancer	26*	5·94	3·75–8·45	1 in 8
Pancreatic cancer	3	1·73	0·34–4·94	1 in 50
Melanoma	2	9·9	1·12–35·7	1 in 50
Stomach cancer	10*	1·97	0·82–3·14	1 in 20
Lung cancer	9	0·57	0·26–1·08	1 in 20

Significance of difference from expected: * $P<0·001$ (Poisson distribution)

showed a reduction of nearly 50 per cent in men with only a small increase in women.

The predominance of cancer of the colon is entirely compatible with the hypothesis of a major gene exerting a primary influence on the development of colon cancer but increasing the liability to tumour development at other sites in the presence of other genetic or environmental events.

Relative risks of cancer for women were significantly greater than for men; this sex disparity was mirrored in the contribution of cancer to all deaths in female relatives. Although this might in part reflect an increased number of target organs for the development of cancer in women (breast, ovary, uterus), it does not explain the generalized increase in relative risk of cancers of the stomach, pancreas and lung in women compared with men. This observation is consistent with an increased gene penetrance in women. A crude estimate of the degree of penetrance obtained by dividing the difference between observed and expected cancer deaths by the total number of observed deaths due to all causes suggests a penetrance of 27 per cent for men and 78 per cent for women.

The frequency of Lynch type II syndrome may be greater than previously thought and, despite the absence of any biomarker, at-risk individuals may readily be identified by examination of their pedigrees. The quantitative information on relative risks and lifetime risks is now available which could influence clinical practice in terms of designing surveillance and screening programmes for individuals at risk. Such programmes, while focusing principally on monitoring the colonic mucosa, should also address the risk of other neoplasms developing, especially in women. Since the increases are not confined to young age groups, any such strategy adopted should be maintained through the lifetime of the individual at risk.

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