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FAMILIAL AGGREGATION OF COLORECTAL CANCER IN THE GENERAL POPULATION

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To investigate the familial aggregation of colorectal cancer in Denmark, parents and siblings of colorectal cancer patients diagnosed below age 60 years in the years 1982–1984 were identified through population registries. For 1,470 probands with families eligible for tracing, 1,376 mothers, 1,303 fathers and 3,259 siblings were identified. They contributed 222,634 person-years, and 325 cases of colorectal cancer were observed during the follow-up period 1943–1992. All data were retrieved from population registries and consequently were free from any reporting bias. The overall standardized morbidity ratio (SMR) compared with the Danish population was 2.02 (95% confidence interval [CI] 1.81–2.25), significantly different between the parents (1.78, 95% CI 1.55–2.04) and the siblings (2.65, 95% CI 2.21–3.17). A strong dependence on the proband's age at diagnosis was seen for the sibling risk; siblings of probands less than 50 years old at diagnosis had a 5-fold risk compared with the general population. This dependence was not seen for parents, but the risk tended to be higher for parents of younger ages. No other factor was seen to influence the relative risk. The observation of an 80% increased risk among the parents and a 170% increased risk among the siblings indicates that the genetic component is one source, but probably not the only one, of familial aggregation of colorectal cancer. The cost benefit of screening siblings of colorectal cancer patients is substantially higher than that for the total population.

Colorectal cancer is the second most frequent cancer disease in developed countries (Parkin *et al.*, 1993). The hereditary syndromes familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNCCP) account for only a minor part of the cases (Burt *et al.*, 1995). There is also, however, a component of familial aggregation (Woolf, 1958; Macklin, 1960; Lovett, 1976; Duncan and Kyle, 1982; Maire *et al.*, 1984; Bonelli *et al.*, 1988; Kune *et al.*, 1989; Fisher and Armstrong, 1989; Ponz de Leon *et al.*, 1989; Stephenson *et al.*, 1991; Søndergaard *et al.*, 1991; St. John *et al.*, 1993; Goldgar *et al.*, 1994; Fuchs *et al.*, 1994) in the population at large. In a population-based, prospective study we found that parents of colorectal cancer patients, in comparison with the general population, had a 75% increased risk of developing the disease (Søndergard *et al.*, 1991). Understanding familial aggregation in colorectal cancer is an important element in the disentangling of the etiology and in the targeting of screening policies. We have therefore extended our study to include the siblings of patients to see whether the risk estimate of 75% can be generalized to all first-degree relatives or whether each generation carries its own risk. As the study is based on the Danish population, for whom incident cancer cases have been registered now for 50 years, a large number of cases furthermore enabled us to "mimic" the clinical situation and estimate the risk for relatives by various characteristics of the proband.

MATERIAL AND METHODS

The study population consisted of the parents and siblings of 1,513 probands diagnosed with colorectal cancer in Denmark in the period 1 January 1982 through 31 December 1984 at ages below 60 years. The follow-up period stretched till the end of 1992. In the previous analysis, the parents were followed till the end of 1986 (Søndergaard *et al.*, 1991).

Tracing of relatives

Relatives could be traced for a total of 1,470 probands as 42 probands were born outside Denmark and only adoptive parents were known for one proband. A total of 1,424 mothers (97%), 1,376 fathers (94% of all, 98% of those where paternity was stated) and 3,396 siblings were traced (Table I).

In Denmark, population registration has been mandatory for local authorities since 1924, though many local population registries started earlier. The tracing probability of fathers and mothers thus depended slightly on the date of birth of the proband (Fig. 1). For mothers, the tracing probability was below 95% only for mothers of probands born before 1927, whereas for fathers, the tracing probability increased gradually by the proband's date of birth. Since parents of younger probands were more likely to be traced and to contribute to the person-years enumeration, there would be a slight over-representation of younger probands in the material. Therefore, to avoid bias, the proband's date of birth (= proband's age at diagnosis as the period of proband ascertainment was short) has been controlled for.

Unlike the number of parents, the number of siblings of a given proband was *a priori* unknown, so there was no simple method of assessing the completeness of the tracing of siblings. Comparison between the obtained distribution of sibship size in the traced families with the distribution of sibship size in the general population can give a picture of the completeness of the tracing of siblings. Provided we consider the probands to be a random sample of survivors from the generations born after 1922, a complete tracing of siblings would provide a distribution of birth number size for the probands similar to that of their respective birth cohorts. Failure to trace all siblings would result in too low birth numbers.

In the calculation we used full siblings and half-siblings through the mother to construct the sibship size of the probands. Figure 2 shows the geometric mean of the birth number for the probands by year of birth compared with that of the population as calculated from the population statistics available from 1931 onward (Danmarks Statistik, 1995). There was a slight deficit of approximately 0.2 in the tracing of the probands' older siblings. The average sibling number was around 2, which means that on average every 10th older sibling was missing. The difference probably reflects the fact that the municipality population registries were established by law in 1924; hence, tracing of siblings born prior to this year was more likely to fail.

Follow-up

The relatives of probands were followed up until death or emigration in the Central Person Registry and for diagnosis of cancer in the Danish Cancer Registry. Persons were followed from the 15th birthday, 1 January 1943 or proband's birth, whichever was latest, through date of death, date of emigration or 31 December 1992, whichever was earliest.

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TABLE I – IDENTIFICATION OF FIRST-DEGREE RELATIVES OF PATIENTS DIAGNOSED WITH COLORECTAL CANCER BEFORE AGE 60 YEARS IN DENMARK 1982–1984

Probands	No.
Patients diagnosed 1982–1984 as identified in 1990[1]	1,525
Presently not fulfilling entry criteria (changed diagnosis, etc.)	7
Sibling of other patient	5
Patients eligible as probands	1,513
Born outside Denmark	42
Only adoptive parents known	1
Patients eligible for tracing of relatives	1,470

Relatives	Mothers	Fathers	Siblings
Paternity not stated	—	59	—
Only adoptive mother/father	1	1	—
Relative identified but untraceable	45	34	113
Relatives traced	1,424	1,376	3,396
Died/emigrated < 1943	48	73	7
Died < 15 years	—	—	129
Sex unknown	—	—	1
Relatives contributing person-years	1,376	1,303	3,259[2]

[1]Number previously reported as 1,524; one patient was incompletely recorded.–[2]Of which 3,058 were full siblings and 201 half-siblings.

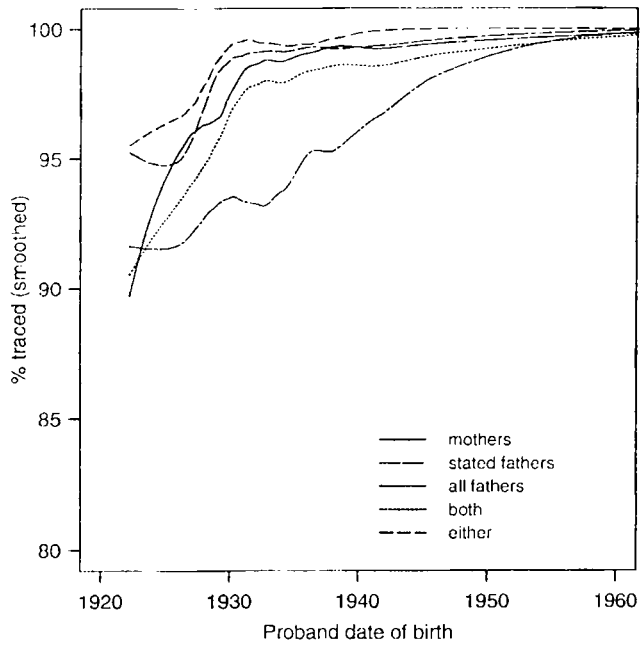

FIGURE 1 – Probability for the tracing of probands' fathers and mothers by proband's age at diagnosis.

Diagnoses of colorectal cancer were recorded for the relatives during the follow-up period. Further, the expected numbers of colorectal cancers during this period were calculated using the incidence rates of the Danish population.

Initially, we calculated standardized morbidity ratios (SMRs) relative to the Danish population, subdivided by various criteria. For the purpose of modeling, the number of colorectal cancer cases, person-years and expected number of cases were tabulated by diagnostic subsite, sex and age at diagnosis of the proband; by sex, current age and previous diagnosis of colorectal cancer of the relative; by years from the proband's birth to the relative's birth; by current date of follow-up, follow-up time in relation to diagnosis of colorectal cancer in the relatives and whether follow-up was before or after the date of diagnosis of the proband.

By the very nature of the data, there was a strong relationship between the proband's and the relative's current age; the major part of the follow-up time for the siblings was from ages 25 to 50 years, whereas the major part for the parents was from ages 55 to 75 years. There was a considerable overlap though (Fig. 3).

Modeling

Incidence rates of colorectal cancer among relatives were modeled as proportional to the population rates, the propor-

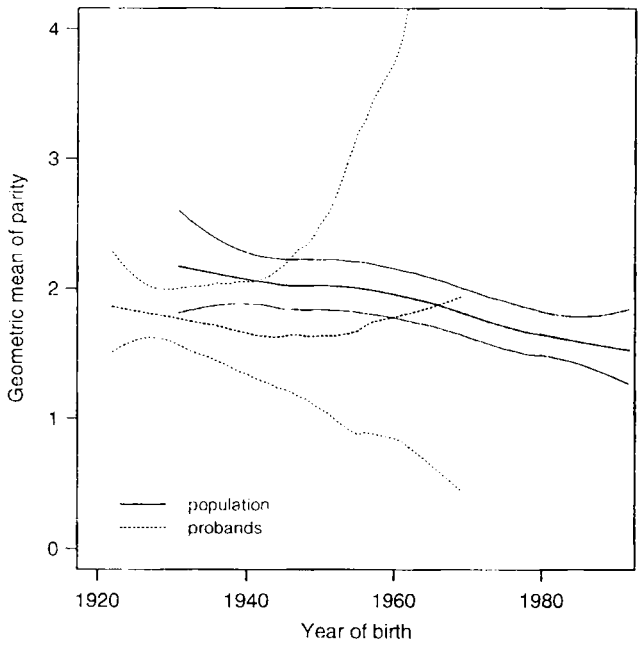

FIGURE 2 – Geometric mean of sibship size for probands and for the Danish population by year of birth. Thin lines indicate 95% confidence intervals.

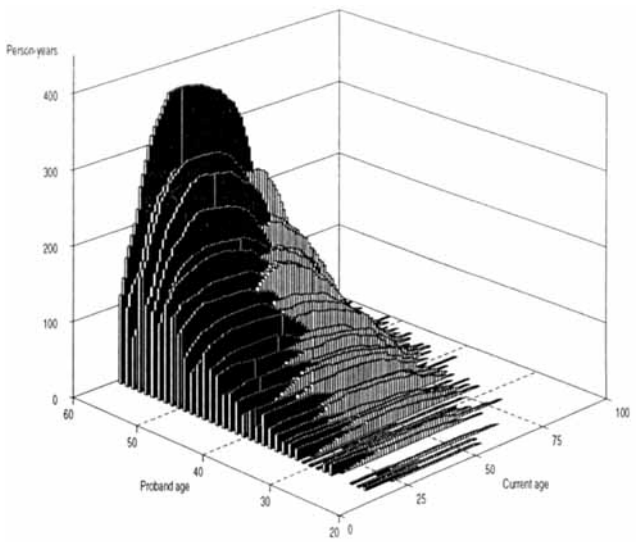

FIGURE 3 – Distribution of follow-up time for parents (light) and siblings (dark) by proband's age at diagnosis and relative's current age.

tionality depending multiplicatively on the combination of variables listed above. The proportional modeling is a generalization of the SMR calculations. If a model with proportionality of rates is fitted with only one factor, the estimates will be the SMRs for each level of that factor.

We also modeled the excess of colorectal cancer incidence rates among the relatives of the probands over the population rates, this excess depending additively on the factors. This procedure corresponds to modeling the rate difference between the relatives and the general population. Both modeling approaches were carried out using a piecewise constant intensity model, leading to Poisson models for the counts of colorectal cancer cases in each cell of the table (Breslow and Day, 1987).

Finally, in addition to the Poisson models involving (linear) effects of the variables leading to relative risk (RR) and excess risk (ER) estimates, we used models where the effects of variables were modeled by an arbitrary smooth function, which was then estimated, the so-called generalized additive models (Hastie and Tibshirani, 1990). This was a useful tool to check whether the effects modeled as linear actually were linear, as well as for exploring the data.

To explore the effects of the relative's current age and the proband's age at diagnosis, we fitted a smooth surface for the RR as a function of these 2 variables. This model was fitted separately for parents and siblings. The surface was fitted using a loess-smoother and the backfitting algorithm as provided by S+ (Hastie and Tibshirani, 1990; Chambers and Hastie, 1991). We furthermore fitted ER models for parents and siblings separately. These models were fitted similarly to the RR models, except that another link function for the Poisson family was provided.

RESULTS

The study population included 5,938 relatives: 1,376 mothers, 1,303 fathers and 3,259 siblings. A total of 222,634 person-years were observed, 88,631 among the parents and 134,003 among the siblings.

The overall SMR for the relatives was 2.02, based on 328 cases, during 222,634 person-years (95% confidence interval [CI] 1.81–2.25). For siblings the SMR was 2.65 (95% CI 2.21–3.17) and for parents 1.78 (95% CI 1.55–2.04). The results of the SMR analysis are shown in Table II. For siblings there was a decrease in SMR by the proband's age at diagnosis but no effect of other variables. For parents there seemed to be some decrease by the parent's current age but not much of an effect by the proband's age at diagnosis. For the other variables there was no remarkable effect.

Multiplicative modeling of the rates rendered all variables other than relation to proband and the proband's age at diagnosis insignificant. However, there was a significant interaction between the relation to the proband and the proband's age at diagnosis. Thus, analysis by the multiplicative models led to a model that in reality was made up from separate models for siblings and parents.

Separate models for siblings and parents were then fitted with all variables; the results are given in Table III. These models could be reduced to models with only the relative's current age and the proband's age at diagnosis. For parents none of these variables was significant, but the parents had the highest risk at younger ages. For siblings the only significant effect was for the proband's age at diagnosis, and there was no remarkable pattern by the sibling's current age.

The contours of the smoothed surfaces of the RRs by the relative's current age and the proband's age at diagnosis are shown in Figure 4. For siblings the dominant feature was lines parallel to the sibling's current age, which means that the RR varied mainly by the proband's age at diagnosis and hardly by the sibling's current age. For parents the RR varied mainly by the parent's current age and not much by the proband's age at diagnosis. The highest RR among the parents was found at the younger ages, which could suggest that a model for ER (rate difference) might be more appropriate than the RR model (rate ratio).

The contours of the ER by relative's current age and proband's age at diagnosis are shown in Figure 5. It can be seen that the ER varied mainly with the relative's current age. There was, however, a small effect of proband's age at diagnosis for siblings, reflecting the fact that the rates of colorectal cancer were small in younger ages.

The plots show that the siblings carried a higher risk than the parents at almost any age and for any proband's age at diagnosis, independent of the scale (ratio or difference) used for the description of the risk relation to the general population.

DISCUSSION

Our study showed a 100% increased risk of colorectal cancer among first-degree relatives of patients with this disease. There was a marked difference between siblings, with a 170% increased risk, and parents, with only an 80% increased risk. Siblings of the patients diagnosed below the age of 50 years had an almost 5-fold increased risk compared with the general population.

Familial aggregation of colorectal cancer has previously been studied mostly in case-control studies, where interviews have been used for the collection of data on family history (Table IV). However, studies of Latter Day Saints (Utah, USA) have used registry data (Goldgar *et al.*, 1994). They found RRs among first-degree relatives between 1.78 and 2.67, depending on subsite of the large bowel. Fuchs *et al.* (1994) studied the cohorts of participants from the US Nurses' Health Study and the Health Professionals Follow-Up Study. After 6–8 years of follow-up, participants who originally reported a family history of colorectal cancer had an RR of this disease of 1.72 compared with the other participants. Our overall SMR of 2.02 is thus close to the results of these 2 studies.

Fuchs *et al.* (1994) observed no difference between the risks for mothers, fathers and siblings. However, their study included 73 "exposed" cases, where the present study includes 325. RRs were higher for siblings than for parents in 4 of the 7 other studies, but these studies were based mainly on interview data and had RRs of up to 7.5.

Our finding of an almost 5-fold increased risk in siblings of patients diagnosed below the age of 50 years is supported by the finding of Goldgar *et al.* (1994) of RRs of 4.0 for colon and 8.0 for rectal cancer for the relatives of probands diagnosed below age 60 years. They also noted that this RR was highest at younger ages but provided no specific information. However, this clinically potentially important finding cannot be further validated as no other study provides data by proband's age at diagnosis.

We have observed a familial aggregation, which may be explained by factors that are common between members of the same family, including genetic factors. If genetic factors were to explain all of the familial aggregation, one would expect that the effect would be the same for the parents and the siblings.

The exception would be a disease caused by a major recessive gene. However, several genes involved in the etiology of colorectal cancer have been described and analyzed (Bodmer *et al.*, 1994; Bishop and Thomas, 1990). Furthermore, if the disease was caused by a single, rare, recessive gene, almost

TABLE II - COLORECTAL CANCER INCIDENCE AMONG FIRST-DEGREE RELATIVES OF PATIENTS DIAGNOSED WITH COLORECTAL CANCER BEFORE AGE 60 IN DENMARK 1982-1984: MARGINAL ANALYSES OF RELATIVE RISK (SMR VALUES) IN THE PERIOD 1943–1992

Variable	Siblings				Parents			
	Obs	Person-years	SMR	95% CI	Obs	Person-years	SMR	95% CI
All relatives	118	134,003	2.65	2.21–3.17	210	88,631	1.78	1.55–2.04
Proband's diagnosis								
Colon, right	33	31,969	3.10	2.13–4.35	48	21,049	1.80	1.32–2.39
Colon, left	34	43,112	2.55	1.76–3.56	76	28,778	2.02	1.59–2.53
Colon, NOS	7	6,105	3.06	1.23–6.31	7	3,202	1.60	0.64–3.29
Rectum	44	52,816	2.41	1.75–3.24	79	35,603	1.60	1.27–2.00
Proband's sex								
Male	67	71,030	2.66	2.06–3.38	111	43,215	1.90	1.56–2.29
Female	51	62,972	2.63	1.96–3.46	99	45,416	1.66	1.35–2.02
Proband's age at diagnosis (yr)								
0–44	8	15,545	4.64	2.00–9.15	30	18,773	1.94	1.31–2.77
45–47	12	10,560	5.69	2.94–9.95	16	8,484	1.62	0.92–2.62
48–50	17	12,656	5.10	2.97–8.16	28	9,535	2.23	1.48–3.22
51–53	16	21,489	2.51	1.43–4.07	43	15,006	2.15	1.56–2.89
54–56	26	34,480	2.01	1.31–2.94	35	17,670	1.25	0.87–1.74
57–59	39	39,272	2.16	1.54–2.96	58	19,164	1.80	1.37–2.33
Years from proband's birth to relative's birth								
< −10	29	16,068	2.57	1.72–3.69	210	88,631	1.78	1.55–2.04
−10–−6	22	18,104	2.46	1.54–3.73				
−6–−2	37	30,298	3.29	2.32–4.53				
−2–2	16	19,750	2.99	1.71–4.86				
2–6	8	25,389	1.58	0.68–3.11				
6–10	4	13,278	2.26	0.60–5.78				
10+	2	11,115	2.32	0.26–8.38				
Relative's sex								
Male	61	65,626	2.75	2.11–3.54	109	39,296	1.83	1.50–2.21
Female	57	68,377	2.55	1.93–3.30	101	49,335	1.73	1.41–2.10
Relative's current age (yr)								
< 50	22	98,742	2.90	1.82–4.39	13	24,075	3.29	1.75–5.62
50–59	31	21,844	2.27	1.54–3.22	29	22,717	2.15	1.44–3.09
60–69	46	11,050	2.80	2.05–3.73	46	21,311	1.52	1.11–2.03
70–79	19	2,304	2.89	1.74–4.52	72	14,659	1.64	1.28–2.06
80+	0	62	—	—	50	5,870	1.89	1.40–2.49
Current date of follow up								
1943–1947	0	8,347	—	—	10	12,311	2.49	1.19–4.58
1948–1952	0	10,954	—	—	7	12,493	1.21	0.49–2.50
1953–1957	0	12,804	—	—	12	12,166	1.53	0.79–2.67
1958–1962	1	14,189	1.21	0.02–6.75	25	11,457	2.20	1.43–3.25
1963–1967	3	15,004	1.94	0.39–5.66	25	10,424	1.76	1.14–2.60
1968–1972	7	15,261	2.45	0.98–5.05	26	9,110	1.55	1.01–2.27
1973–1977	14	15,195	2.91	1.59–4.88	29	7,554	1.58	1.06–2.28
1978–1982	19	14,864	2.48	1.49–3.87	30	5,934	1.76	1.19–2.52
1983–1987	36	14,211	3.17	2.22–4.39	29	4,311	2.10	1.41–3.02
1988–1992	38	13,175	2.59	1.83–3.55	17	2,871	1.90	1.10–3.04
Follow-up in relation to date of proband's diagnosis								
Before	44	108,037	2.27	1.65–3.04	168	81,935	1.74	1.48–2.02
1st year after	9	2,890	4.47	2.04–8.48	3	955	1.01	0.20–2.95
2nd–4th year after	65	13,079	5.26	4.06–6.70	39	3,680	3.27	2.33–4.47
5th year + after	0	9,996	—	—	0	2,061	—	—
Follow-up in relation to diagnosis of colorectal cancer in relative								
Before	112	133,516	2.55	2.10–3.07	203	87,874	1.75	1.52–2.01
After	6	487	9.63	3.52–20.96	7	758	3.38	1.35–6.95

all probands with the genetically determined disease would be children of 2 heterozygous parents and the parents would then carry little or no ER. The parents did, however, also have an ER of colorectal cancer.

The observation then of a 170% increased risk among the siblings and an 80% increased risk among the parents thus indicates that the genetic component is one source, but probably not the only one, of the familial aggregation. While

TABLE III – COLORECTAL CANCER INCIDENCE AMONG FIRST-DEGREE RELATIVES OF PATIENTS DIAGNOSED WITH COLORECTAL CANCER BEFORE AGE 60 YEARS IN DENMARK 1982–1984: RESULTS OF MULTIPLICATIVE MODELING OF RATES

Variable	Siblings		Parents	
	RR	95% CI	RR	95% CI
Baseline relative risk[1]	1.96	0.85–4.55	1.44	0.86–2.40
Proband's diagnosis				
Colon, right	1.24	0.78–1.95	1.15	0.80–1.65
Colon, left	1.01	0.64–1.59	1.29	0.94–1.77
Colon, NOS	1.26	0.56–2.81	0.99	0.45–2.14
Rectum	1.00	—	1.00	—
Proband's sex				
Male	1.04	0.71–1.52	1.18	0.90–1.56
Female	1.00	—	1.00	—
Proband's age at diagnosis (yr)				
0–44	3.48	1.29–9.41	0.90	0.54–1.48
45–47	3.82	1.71–8.52	0.83	0.47–1.47
48–50	3.14	1.60–6.14	1.15	0.72–1.82
51–53	1.38	0.73–2.58	1.13	0.76–1.69
54–56	1.04	0.62–1.74	0.68	0.44–1.04
57–59	1.00	—	1.00	—
Years from proband's birth to relative's birth				
< −10	1.00	—	1.00	—
−10–−6	1.27	0.69–2.34		—
−6–−2	2.01	1.06–3.82		—
−2–2	2.11	0.92–4.85		—
2–6	1.30	0.45–3.74		—
6–10	1.93	0.50–7.44		—
10+	2.14	0.37–12.44		—
Relative's sex				
Male	1.12	0.78–1.61	1.14	0.86–1.51
Female	1.00	—	1.00	—
Relative's current age (yr)				
<50	0.40	0.10–1.58	2.22	1.15–4.27
50–59	0.38	0.14–0.99	1.42	0.88–2.31
60–69	0.64	0.33–1.24	0.97	0.66–1.44
70+	1.00	—	1.00	—
Current date of follow-up				
1967	1.05	0.42–2.64	0.84	0.53–1.35
1968–1977	1.47	0.71–3.05	0.88	0.52–1.46
1977–1982	1.00	—	1.00	—
1983–1987	0.65	0.22–1.91	1.26	0.48–3.26
1988–1992	0.43	0.13–1.44	1.03	0.33–3.25
Follow-up in relation to date of proband's diagnosis				
Before	1.00	—	1.00	—
1st year after	2.38	0.82–6.96	0.47	0.12–1.84
2nd + year after	1.67	0.54–5.19	1.05	0.39–2.82
Follow-up in relation to a second diagnosis of colorectal cancer in relative				
Before	1.00	—	1.00	—
After	3.38	1.47–7.79	1.89	0.88–4.05

[1]The baseline relative risk is for a woman who is parent/sibling to a female rectal cancer proband 57–59 years old at diagnosis, born more than 10 years before the proband, current age > 70, current date 1988–1992 and followed before the diagnosis of the proband and after the diagnosis of the first colorectal cancer.

members of the same family are exposed to the same environment in terms of, *e.g.*, diet, this common exposure is naturally strongest in the period when the family members live together. For the parent–proband relation this covers vastly different age segments of life, whereas for the siblings–proband relation it occurs at similar ages.

We therefore explored the effect of the difference in date of birth between the proband and the siblings. If the proband and the sibling(s) were born closely after each other, one would expect a greater similarity in, *e.g.*, diet than if their birth dates were further apart. We found, however, no characteristic pattern in the variation of RR with this variable (Tables II, III).

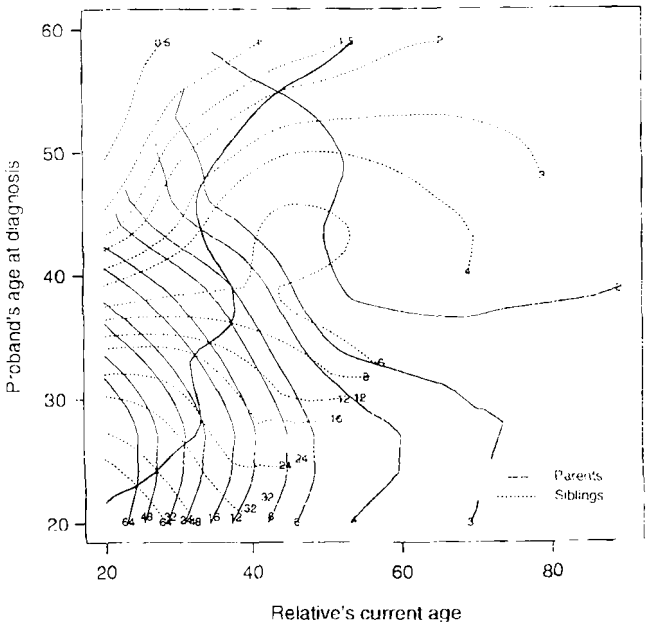

FIGURE 4 – Relative risks of colorectal cancer among parents and siblings by proband's age at diagnosis and relative's current age. (See text for explanation of contours of the RR).

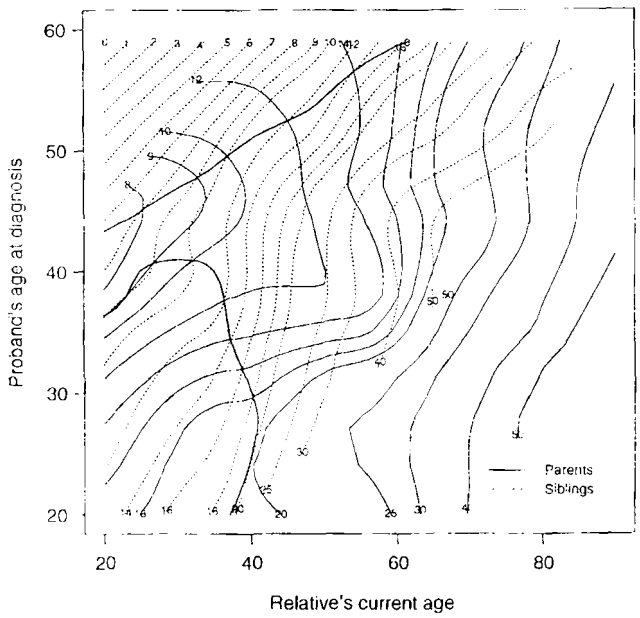

FIGURE 5 – Excess risks of colorectal cancer among parents and siblings by proband's age at diagnosis and relative's current age. (See text for explanation of contours of the ER).

TABLE IV – RELATIVE RISKS (RRs) OF COLORECTAL CANCER IN STUDIES OF FIRST-DEGREE RELATIVES OF PATIENTS WITH THE DISEASE

Population	Period of case recruitment	Design	Ascertainment of relatives diagnosed	Total observed	RR	Parents		Siblings		References
						Obs	RR	Obs	RR	
United States										
Utah, Latter Day Saints	1931–1951	Case-control	Registry data	26	3.33	10	10.32	16	2.33	Woolf, 1958
Utah, Latter Day Saints	1952–1992	Relatives of patients compared to relatives of non-patients	Registry data	334 36 97	2.67 1.78 1.97	(patient colon, relative colon) (patient rectum, relative rectum) (patient rectum, relative colon)				Goldgar *et al.*, 1994
Ohio	1952–1955	Proportional mortality analysis	Interviews confirmed by death certificates	31	3.2	17	3.3	14	3.1	Macklin, 1960
Nurses' Health Study and Health Professionals' Study	1982–1990 1986–1992	Cohort of relatives of patients	Questionnaires confirmed by hospital records	73	1.72	No difference between mothers, fathers and siblings				Fuchs *et al.*, 1994
Australia										
Metropolitan Melbourne	1980–1981	Case-control	Interview	123	2.13	72	1.93	58	2.50	Kune *et al.*, 1989
Alfred Hospital, Melbourne	1952–1985 (survivors by 1986)	Case-control	Interview	110	2.1	61	2.4	53	1.9	St. John *et al.*, 1993
Bunbury, Western Australia	1975–1984	Case-control	Interview, confirmed by death certificate and medical records	10	2.5					Fisher and Armstrong, 1989
Europe										
St. Mark's Hospital, London, UK	1969–1973	Proportional mortality analysis	Interview	41	3.52	23	2.78	18	5.34	Lovett, 1976
Aberdeen, UK	Not reported	Case-control	Interview confirmed by medical records	8	9.03					Duncan and Kyle, 1982
Leeds, UK	Not reported	Cohort of relatives of patients	Interview confirmed by medical records	18	4.4					Stephenson *et al.*, 1991
Poitiers, France	1979–1983	Case-control	Interview	31	6.1	20	4.4	11	11.69	Maire *et al.*, 1984
Genoa, Italy	1980–1986	Case-control	Interview	47	2.36					Bonelli *et al.*, 1988
Modena, Italy	1984–1986	Case-control	Interview	89	7.5	27	4.2	60	14.7	Ponz de Leon *et al.*, 1989
Denmark	Probands 1982–1984 Relatives 1943–1992	Cohort of relatives of patients	Registry data	328	2.02	210	1.78	118	2.65	Present study

Confidence intervals in our present study were calculated with the assumption that the individuals in the follow-up were independent. As they actually come from the same families, they are not independent if there are family-specific genetic or environmental factors influencing the risk, and the calculated confidence intervals are therefore slightly too narrow.

Clinical implications

As the RR of colorectal cancer is as high as 5 for siblings of colorectal cancer patients diagnosed at ages below 50 years, one might argue that this population should be offered intensive screening for colorectal cancer, irrespective of the nature of the pre-disposing factors for colorectal cancer being mainly genetic or environmental. If environmental factors are predominant, then the probands would simply point to persons (siblings) with a high likelihood of sharing the crucial risk factors.

To further explore this point, we simulated a clinical situation by restricting the follow-up of siblings to the period after the diagnosis of the proband. This corresponds to the ascertainment of siblings that one would actually find in daily clinical practice.

We found that SMRs were higher in the period after the diagnosis of the proband. The SMR for parents was 1.74 before and 1.97 after the diagnosis of the proband, and for the siblings we found a change in the SMR from 2.27 to 2.95. This could point to a screening effect, but the higher risk was not restricted to the period following immediately the proband diagnosis (Table II).

Figure 6 shows the cumulative incidence rate of colorectal cancer among siblings of colorectal cancer patients, counting only the experience subsequent to the proband's diagnosis. For the siblings the cumulative incidence rate was around 5% at age 50 years and around 10% at age 60 years, roughly independent of the proband's age at diagnosis.

Denmark is a typically developed country with an age-standardized rate of colorectal cancer (world standard population per 100,000) of 38 for men and 30 for women (Parkin *et al.*, 1992). Given a patient diagnosed with colorectal cancer before the age of 50 years, a 40-year-old sibling in this Danish population has a 13.5% probability of developing colorectal cancer over the next 30 years (assuming zero mortality), whereas the corresponding figure for a randomly chosen 40-year-old person from the population is 3.7%. The 30-year probability for a 40-year-old sibling is thus 3.5 times the population probability. In Denmark, 300 siblings would be recruited within 1 year (*i.e.*, 200 new colorectal cancer patients below age 50 years × 1.5 siblings per patient), and they would be expected to develop some 40 colorectal cancers over the next 30 years. The entire generation of 75,000 40-year-old Danes would develop 2,700 colorectal cancers over the next 30 years. With a screening program aimed at siblings, it would thus be possible to target some 2% of the colorectal cancers with less than 1% of the resources required for population screening. The cost-benefit of sibling screening would thus be considerably higher than the cost-benefit of population screening but would not be the solution to the colorectal cancer public health problem.

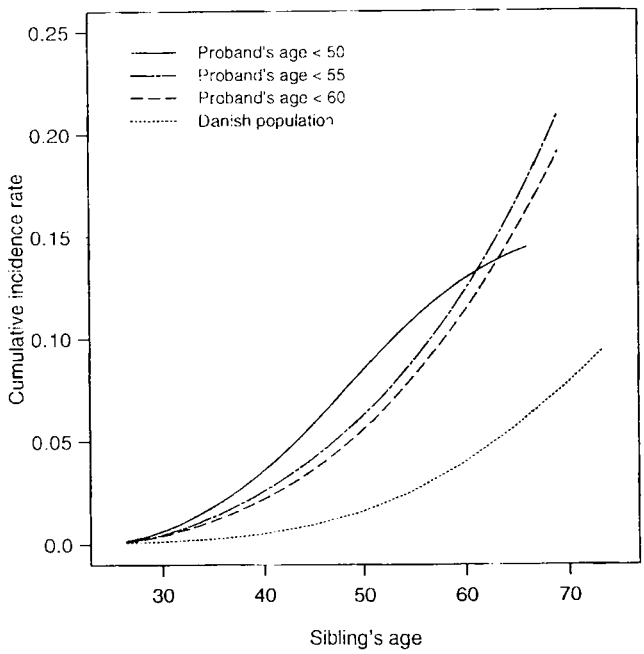

FIGURE 6 – Cumulative incidence rate (= cumulative risk) for siblings of probands, using only follow-up after the diagnosis of the proband and cumulative incidence rate for the Danish population. Note: the groups are not mutually exclusive. Calculations are based on a model that describes the incidence rates as a smooth function of current age. The curves are integrals of the resulting estimated rates.

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