Pergamon

European Journal of Cancer, Vol. 35, No. 8, pp. 1248–1257, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00135-5

Original Paper

Incidence of Malignant Tumours in Relatives of *BRCA1* and *BRCA2* Germline Mutation Carriers

O. Johannsson,[1*] N. Loman,[1*] T. Möller,[2] U. Kristoffersson,[3] Å. Borg[1] and H. Olsson[1]

[1]Department of Oncology; [2]Regional Tumour Registry; and [3]Clinical Genetics, University Hospital Lund, S-221 85 Lund, Sweden

We investigated cancer incidence between 1958 and 1995 in 1873 individuals belonging to 29 consecutively identified *BRCA1* and 20 *BRCA2* associated families from Southern Sweden using data from parish and local tax authorities, as well as the Swedish Cancer Registry, Cause of Death Registry and Census Registry. 150 malignant tumours were analysed from 1145 relatives in the *BRCA*1 families and 87 tumours were analysed from 728 relatives in the *BRCA2* families. After excluding index cases which led to the mutation analysis, the incidence for all malignant tumours was significantly increased for both *BRCA1*- standardised morbidity rate, SMR, 1.98, 95% confidence interval (CI) 1.59–2.45; $P<0.0001$ and *BRCA2*- (SMR 1.79, 95% CI 1.35–2.31; $P<0.0001$) associated family members. For women in *BRCA1*-associated families, the incidence of breast cancer (SMR 3.76, 95% CI 2.29–5.80, $P<0.0001$), ovarian cancer (SMR 15.49, 95% CI 9.46–23.92, $P<0.0001$), stomach cancer (SMR 5.86, 95% CI 1.60–15.01, $P=0.005$) were significantly increased. Amongst men only invasive squamous cell cancer of the skin was significantly increased (SMR 6.02, 95% CI 1.96–14.05, $P=0.002$). In *BRCA2* associated families, female breast cancer (SMR 3.03, 95% CI 1.61–5.18, $P=0.0005$) was increased after exclusion of index cases. If these were included, ovarian cancer (SMR 5.16, 95% CI 1.89–11.24, $P=0.001$), invasive cervical cancer (SMR 4.21, 95% CI 1.15–10.79, $P=0.016$), male breast cancer (SMR 290.52, 95% CI 125.42–572.43, $P<0.0001$), and prostate cancer (SMR 2.21, 95% CI 0.89–4.56, $P=0.042$) were significantly increased. The increased risk for ovarian cancer in *BRCA2* related families were limited to the cases leading to mutation analysis. Our data suggest that apart from breast and ovarian cancer, the incidence of other cancer types do not appear to be greatly increased in *BRCA1*- and *BRCA2*-associated families and does not warrant specific clinical follow-up in carriers. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, ovarian cancer, male breast cancer, *BRCA1*, *BRCA2*, hereditary cancer, cancer incidence
Eur J Cancer, Vol. 35, No. 8, pp. 1248–1257, 1999

INTRODUCTION

GERMLINE MUTATIONS in the *BRCA1* and *BRCA2* genes are thought to cause the great majority of inherited breast and ovarian cancer [1]. The risk of developing other cancer types may also be increased. For *BRCA1* the risk for cancer of the colon [2] and prostate [2, 3] have been reported as being significantly increased, leading to the suggestion that these cancer types should be considered when decisions regarding surveillance are taken [4]. For *BRCA2*, risk of pancreatic, stomach, uterus and prostate cancer, as well as hepatomas, melanoma of the skin and rarer forms such as ocular melanoma have been reported to be increased in epidemiological studies or been associated with germline mutations in tumour specimens [5–14].

As most of these studies have been gathered from families identified and evaluated for research purposes during the search for the *BRCA1* and *BRCA2* genes and, therefore, by design represented by large multicase families, the application of this data for patients identified from the general population has been questioned. Indeed, the overall cumulative lifetime risk of breast cancer among carriers of a *BRCA1* mutation, reported to be approximately 85% [1, 15, 16] has in a more

* To be considered joint first authors.
Correspondence to O. Johannsson, e-mail: oskar.johannsson@onk.lu.se
Received 14 Dec. 1998; revised 6 May 1999; accepted 23 May 1999.

recent study on families not collected for the purpose of finding the two genes been estimated to be lower [17]. Furthermore, most of the available data used to estimate risk for other malignancies in *BRCA1*-associated families is based on linkage studies of high risk families, suggesting that these data may also be not fully representative for patients identified from the general population. In addition, since *BRCA1* germline mutations have not been found in all families believed to be linked to *BRCA1* and, conversely, found in some believed not to be linked [1, 18–20], the use of data from linkage analysis of high risk families may lead to erroneous estimates. As the identification of carriers of *BRCA1* and *BRCA2* germline mutations is becoming more commonplace in a clinical setting, it is of great importance to reconsider what tumour types other than breast and ovarian cancer might require clinical follow-up, surveillance or prophylactic measures, in order to decrease cancer morbidity in these families. We, therefore, performed a study on the incidence of malignant tumours among family members belonging to Swedish *BRCA1*- and *BRCA2*-associated kindreds.

PATIENTS AND METHODS

Study population and mutation analysis (Tables 1 and 2): from October 1994 to the end of July 1997 a total of 29 *BRCA1* and 20 *BRCA2* germline mutation carrying probands residing within the South Swedish healthcare region were identified. These were identified based on different criteria:

(a) Patients with a family history of breast and/or ovarian cancer identified by clinicians from the Departments of Oncology and Clinical Genetics at the joint Oncogenetic outpatient clinic at the University Hospital of Lund or as research families collected at the department of Oncology. To be considered for *BRCA1*/*BRCA2* mutation analysis, the family had to encompass at least 3 first degree relatives affected with breast or ovarian cancer whereof at least one was diagnosed before the age of 50 years, or 2 first degree relatives whereof at least 1 was diagnosed before the age of 40 years. Patients with breast or ovarian cancer before the age of 30 years were also considered for mutation analysis. In addition, families with a case of male breast cancer was considered for *BRCA2* mutation screening The family members thus identified were classified as index patients.

(a)[1] Individuals from two families originally collected for *BRCA1* linkage studies in 1993–1994. For this study

Table 1. *Characteristics of* BRCA1 *related families*

Family	Mutation	Individuals (relatives)*	Selection criterion†	Branch 1 excluded	Reason for exclusion 1	Branch 2 excluded	Reason for exclusion 2
Lund 1	Lod 1,56	105 (74)	(a)[1]	m	f linkage	pgf	pgm linkage
Lund 3	2594delC	79 (73)	(a)[1]	m	f linkage	pgf	pgm linkage
Lund 8	1201del11	33 (23)	(a)	f	m (MC)	pgf	pgm (BC)
Lund 9	C1806T	86 (62)	(b)	f	m (MC)	mgf	mgm (BC)
Lund 24	3166ins5	49 (38)	(a)	f	m (MC)	mgf	mgm (OC)
Lund 30	T300G	78 (53)	(b)	f	m (MC)	mgm	mgf (MC)
Lund 33	G5272-1C	59 (42)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 36	C1806T	9 (3)	(a)	m	f (MC)	mgf	mgm (MC)
Lund 44	3166ins5	39 (27)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 49	1675delA	71 (57)	(a)	m	no early onset BC/OC	f	no early onset BC/OC
Lund 54	2401delAA	27 (19)	(a)	m	f (MC)	pgf	pgm + 2sisters(BC)
Lund 56	C1806T	79 (58)	(a)	m	f (MC)	mgf	mgm sisters (BC/OC)
Lund 66	1201del11	14 (8)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 79	1201del11	39 (28)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 85	2594delC	34 (24)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 93	2594delC	196 (138)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 107	2594delC	89 (63)	(a)	m	no early onset BC/OC	f	no early onset BC/OC
Lund 133	G1177A	172 (121)	(b)	m	f (MC)	pgm	pgf (MC)
Lund 134	3166ins5	129 (93)	(b)	f	m (MC)	mgf	(BC/OC) among relatives of mgm
Lund 141	2594delC	55 (35)	(a)	f	m (MC)		
Lund 149	3166ins5	7 (4)	(a)	f	m (MC)	mgm	mgm (MC)
Lund 166	1675delA	33 (17)	(a)	f	m (MC)	mgf	(BC/OC) among relatives of mgm
Lund 171	2594delC	46 (32)	(a)	f	m (MC)	mgf	mgm (MC)
Lund 193	1049delG	8 (6)	(a)	f	m (MC)	mgf	mgm (early onset BC)
Lund 212	C1806T	18 (11)	(a)	f	m (MC)		
Lund 223	C1806T	13 (9)	(a)	f	m (MC)	mgf	mgm + 2 sisters (BC)
Lund 263	3829delT	9 (7)	(b)	f	m (MC)	mgf	(BC/OV) among relatives of mgm
Lund 264	C1806T	8 (6)	(b)	f	m (MC)	mgf	mgm + 2 sisters (OC)
Lund 265	1201del11	10 (9)	(b)	f	m (MC)	mgm	(BC/OC) among relatives of mgm
SUM		1594 (1145)					

*Total number of individuals in the family, number of relatives in brackets. (Difference refers to number of spouses.) †(a) Family identified in the Oncogenetic reception, at least 3 affected first degree relatives with breast or ovarian cancer whereof at least one diagnosed before the age of 50, or 2 first degree relatives whereof one diagnosed before age 40, or a single case of breast or ovarian cancer diagnosed before the age of 30. (a)[1] The same criteria as (a), but originally collected for linkage study. (b) Family identified through population based study in Southern Sweden of early onset breast cancer (<= 40) 1990–1995. (c) Family identified among consecutive cases of male breast cancer. (d) Family identified among consecutive cases of epithelial ovarian cancer. m, mother of proband; f, father of proband; mgm, maternal grandmother of proband; mgf, maternal grandfather of proband; pgf, paternal grandfather; pgm, paternal grandmother; BC, breast cancer; OC, ovarian cancer; MC, mutation carrier.

Table 2. Family characteristics of BRCA2 *related families*

Family	Mutation	Individuals (relatives)*	Selection criterion†	Branch 1 excluded	Reason for exclusion 1	Branch 2 excluded	Reason for exclusion 2
Lund 10	4486delG	41 (34)	a	m	f (MC)	pgm	(BC/OC) among relatives of pgf
Lund 11	4486delG	18 (11)	b, fulfils criteria of a	f	m (MC)	pgf	(BC/OC) in pgf + 2 of her 4 sisters and mother.
Lund 29	2024del5	162 (112)	b, fulfils criteria of a	mgf	mgm (MC)		
Lund 46	A3058T	84 (61)	a	f	m (MC)		
Lund 53	4265delCT	1 (1)	a	Both parents	No data available		
Lund 91	5392delAG	17 (12)	a	Both parents	Immigrant		
Lund 119	5445del5	275 (194)	b, fulfils criteria of a	m	f (MC)		
Lund 131	9636delT	28 (20)	a (+ c‡)				
Lund 146	C7786T	50 (35)	a	f	m bilateral (BC) age 30 years		
Lund 175	9808delCC	30 (22)	a	f	m (MC)		
Lund 225	C6293G	9 (7)	a				
Lund 237	C7180T	14 (11)	a				
Lund 292	6503delTT	21 (15)	c				
Lund 293	9326insA	15 (10)	c				
Lund 294	4486delG	47 (33)	c				
Lund 295	4486delG	30 (22)	c				
Lund 296	4486delG	48 (37)	c				
Lund 297	G4186T	50 (35)	c				
Lund 304	4079delGT	67 (49)	d				
Lund 305	6174del5	10 (7)	d	Both parents	Immigrant		
SUM		1017 (728)					

*Total number of individuals in the family, number of relatives in brackets. (Difference refers to number of spouses.) †(a) Identified in the Oncogenetic reception, at least 3 affected first degree relatives with breast or ovarian cancer whereof at least 1 diagnosed before the age of 50, or 2 first degree relatives whereof one diagnosed before age 40, or a single case of breast or ovarian cancer diagnosed before the age of 30 years. (b) Identified through population based study in Southern Sweden of early onset breast cancer (<= 40) 1990–1995. (c) Identified among consecutive cases of male breast cancer. (d) Identified among consecutive cases of ovarian cancer. ‡This family was identified after oncogenetic counseling of a woman whose father and mother had had breast cancer aged 64 and 46 years respectively. m, mother of proband; f, father of proband; mgm, maternal grandmother of proband; mgf, maternal grandfather of proband; pgf, paternal grandfather; pgm, paternal grandmother; BC, breast cancer; OC, ovarian cancer; MC, mutation carrier.

the proband and those of her first degree relatives diagnosed with breast cancer before the age of 50 years were classified as index patients. In one of these families (Lund 3) a *BRCA1* germline mutation was later identified (2594delC).

(a + a[1]: 27 *BRCA1* related families, 12 *BRCA2* related families).

(b) Breast cancer patients participating in an ongoing population based study of the frequency of *BRCA1* and *BRCA2* germline carriers among all early onset breast cancer cases (age $\leq$40 years at diagnosis) in Southern Sweden in 1990–1995 ($n = 264$). In this study 232 (88%) of the total population were included. (7 individuals with *BRCA1* mutations where the family of 1 did not fulfil the criteria in (a), 3 individuals with *BRCA2* mutation where the families all fulfilled the criteria in (a) were included in the present study.)

(c) Male breast cancer cases tested positive for *BRCA2* mutations. These men were identified in a hospital-based material of 35 cases collected in 1971–1989 and consisting of approximately 42% of all male breast cancers in Southern Sweden during the period (6 individuals, none of whose family fulfilled the criteria in (a) [21]. One other male breast cancer case (131) was included in the study, but he was identified according to the criteria in (a) based on breast cancer in a man and his mother at ages 64 years and 46 years, respectively.

(d) Ovarian cancer cases tested positive for *BRCA2* germline mutations. These women were identified in a hospital-based material of 37 cases of epithelial ovarian cancer (2 individuals, none of whose families fulfilled the criteria in (a)).

All cases in the population based sample (b) and the hospital based samples (c) and (d) were screened for germline mutations in *BRCA1* and *BRCA2*, sample (b) or *BRCA2* only samples (c) and (d), irrespective of the family history.

The index patients are those patients that helped in identifying the family and leading to its participation in mutation analyses. The study population consisted of identified relatives to these index individuals (see pedigree expansion). In the families identified according to (c) or (d), and in the family in (b) that did not fulfil the criteria in (a), only the proband was classified as the index patient. The index patients in group (a), according to the definitions above, were identified due to a clustering of cancer cases within the family. This clustering can be due to the mutation identified or be due to some other modifying factor (genetic or environmental) that theoretically may only apply for this branch of the family. In order to minimise this effect, the calculations in the study were performed twice, first including the index patients and then a second time after excluding them.

Furthermore, in order to avoid unnecessary dilution of non-mutation carriers, branches that were judged or proved not to harbour the mutation were excluded. These exclusions and motives for them are listed in Tables 1 and 2.

The methods used to identify *BRCA1* and *BRCA2* germline mutations have been previously described [21–23].

Pedigree expansion

All information provided by the probands regarding family size and cancer incidence was controlled. Extensive pedigrees were constructed by means of contacting the local parish or the local revenue authorities that keep the local census registries. By these means, spouses, children/siblings and parents of probands were identified. In the next round, children of these were identified, as well as grandparents, grandparents siblings and great-grandparents and then their children, spouses and grandchildren. In this manner the families were traced back to the generation born in the mid 19th century, most often 1850–1870. Though it is possible to trace the families further back, this was not performed, as this would have led to an underestimation of tumours as hospital and cause of death records are only available for those that survived into this century. This would add difficulties in judging which branch of the family harbours the mutation. More importantly, the Central Cancer Registry for the whole of Sweden was not established until 1958. Therefore, in order to obtain a homogenous sample, only those family members alive in and after 1958 and not born later than 1995, and only those tumours that occurred in the Registers between 1958 and the end of 1995 were included in the statistical studies. For immigrants to Sweden, only those branches of the families that reside within Sweden were entered into the study. This applied to 3 *BRCA2*-associated families (91, 293 and 305). In only 1 family (53) information was not provided due to lack of information at the local parish register. Families were expanded on both parental and maternal sides. For the purpose of this study, only the side of the family believed or proved to harbour the *BRCA1* and *BRCA2* mutation was used for analyses. In most cases this was possible due to verified mutations in relatives of the index individual. However, when nobody was tested outside the index group, we based our assumptions of the origin of the mutation on the prevalence of breast and/or ovarian cancer at young age within a branch of the family. There were doubts on the origin of the mutation in branches of 2 *BRCA1* families. In each instance both branches were excluded from the analyses. In the *BRCA2*-related families identified through cases of male breast cancer, the origin of the mutation was unclear due to lack of positive hereditary history for breast cancer of the index person in six out of seven cases. Therefore, for all families of male breast cancer probands both main branches of the pedigree were included in the study in order not to overlook possible repeatedly occurring tumour types. As we were prohibited from contacting distant family members other than those the proband was willing to establish contact with first, only a limited number of living family members have to date been analysed for mutations. Similarly, due to ethical limitations on the ascertainment of a germline mutation in a deceased individual, where informed consent could not be obtained, we could not use stored pathological specimens from cancer or non-cancer tissue to establish or verify the presence of a *BRCA1* or *BRCA2* mutation, unless permission by close (first degree) relatives was given. This makes it impossible at present to estimate definite cancer risk for mutation carriers and non-carriers within the families. The rates observed, therefore, apply for the branch of the family as a whole (mutation carriers and non-mutation carriers together) compared with spouses and the general population.

In the sample, 1386 out of 2599 individuals (relatives and spouses) were born before 1961 (53.3%), in these individuals 294 out of 302 tumours (97.4%) occurred.

Statistical analysis

All family members and spouses thus identified and alive on 1 January 1958 were followed from then onwards in the population-based Census Registry (to 30 November 1997 and the Swedish Cancer Registries to 31 December 1995). The entry date January 1, 1958 is the date when the Swedish Cancer registry was established and the closure date reflects that national cancer incidence data are currently only available nationwide until the end of December 1995. The vital status and residence was determined until end of December 1995. Tumours occurring in these families before or after the study period were not included. The same applies to cases known to us through case- or pathological reports that were not identified in the national cancer registry. This occurred if either the case had never been reported to the cancer registry or the person identification number was insufficient or wrong. These cases where excluded in order to avoid a selection bias favouring a higher cancer incidence among individuals in the families compared with the general population. Each individual could have more than one tumour registered, but only the first two diagnoses were entered into the analysis due to limitations in the software used. Only malignant tumours were included. Observed versus expected tumours were calculated for the various tumour types using age-, gender-, and calendar-year specific reference data from the whole of Sweden. The calculation used the person-years method, classifying individuals into 5-year age groups and single calendar years as the unit cell size. 21 subjects were lost to follow-up due to emigration. Cause-specific standardised morbidity rates (SMR) and 95% confidence intervals (CI) were calculated. *P* values were calculated using the Poisson distribution or the Chi-square distribution if the expected values were greater than 10. *P* values <0.05 were considered significant. All tests were two-tailed.

RESULTS

BRCA1

In all, 176 malignant tumours occurred among 1145 relatives (549 males and 596 women) in the *BRCA1* families. 13 of these occurred prior to 1958 or after 1995. Another 7 were not identified in the Central Cancer Registry, and 3 cancers were known to have occurred in individuals that had emigrated from Sweden during the study period. Furthermore, as only the first two cancer diagnoses were used three tumours (two ovarian cancers and one breast cancer) were not included. Thus, 150 tumours from 128 individuals (22 men and 106 women) were entered into the analysis. Of these 128 individuals, 106 (19 men and 87 women) had one tumour diagnosis, 3 men and 19 women had two or more tumour diagnoses.

Ovarian cancer was found in all but 5 families, 2 of whom contained tumours that might have been ovarian cancers, i.e. a patient in family 66 diagnosed with abdominal dissemination (including the ovaries) of a cancer classified as a stomach

Table 3. *Tumour incidence among* 596 *females (*14 361.6 *person-years) belonging to* BRCA1*-associated families (*539 *women or* 12 709.4 *person-years when index cases were excluded)*

		All					Index excluded				
ICD-7	Type	Obs.	Exp.	SMR	95% CI	*P* value	Obs.	Exp.	SMR	95% CI	*P* value
140–209	All Malignant tumours	125	23.75	5.26	4.38–6.27	<0.0001	59	20.47	2.88	2.19–3.72	<0.0001
151	Stomach	4	0.77	5.16	1.41–13.22	0.008	4	0.68	5.86	1.60–15.01	0.005
153	Large bowel	1	1.52	0.66	0.02–3.66	1.0	1	1.34	0.75	0.02–4.17	1.0
154	Rectum	3	0.73	4.12	0.85–12.03	0.038	3	0.64	4.71	0.97–13.77	0.027
157	Pancreas	2	0.56	3.58	0.43–12.94	0.108	2	0.49	4.06	0.49–14.67	0.088
162	Lung	2	0.72	2.76	0.33–9.97	0.165	2	0.63	3.19	0.39–11.53	0.131
170	Breast	60	6.26	9.59	7.32–12.35	<0.0001	20	5.32	3.76	2.29–5.80	<0.0001
172	Uterine body	1	1.39	0.72	0.02–4.0	1.0	0	1.19	0	0–3.09	0.636
175	Ovary	43	1.52	28.38	20.54–38.23	<0.0001	20	1.29	15.49	9.46–23.92	<0.0001
176	Vulva	1	0.19	5.39	0.14–30.0	0.169	1	0.16	6.18	0.16–34.45	0.149
190	Melanoma	2	0.90	2.22	0.27–8.01	0.228	2	0.76	2.62	0.32–9.47	0.178
191	Skin	1	0.4	2.36	0.06–13.13	0.346	1	0.37	2.72	0.07–15.15	0.308
193	CNS	1	1.19	0.84	0.02–4.67	1.0	1	1.04	0.96	0.02–5.34	1.0

Note: Only ICD sites for tumours found among *BRCA1*-associated family members are shown. Obs., observed number of cases; Exp., Expected number of cases; SMR, standardised morbidity ratio; CI, confidence interval; CNS, central nervous system.

cancer, though it was suggested in the pathological record that it might have originated in the ovaries. The same applies to the three tumours of unknown origin. In all cases these were abdominal disseminated tumours where ovarian origin was suggested, among other possibilities. Though no formal cluster analysis was performed there is little to suggest any significant clustering of other tumour types within individual families or germline mutation. The only tumours found in more than 1 individual of the same family were breast and ovarian cancer, apart from two cases of skin cancer in family 79 and two cases of prostate cancer in family 171. Interestingly, four out of six stomach cancers occurred in individuals from 4 separate families that shared the same Swedish *BRCA1* founder germline mutation, 2594delC.

In Tables 3–5, observed versus expected cancer cases are represented and the calculated SMR values shown. For women belonging to *BRCA1* associated families (Table 3) there was a significant excess of all cancers (125 observed (obs.) versus 23.75 expected (exp.), SMR 5.26, $P<0.0001$). With regard to individual tumour types, there was a significant increase in breast cancer (60 obs. versus 6.26 exp.; SMR 9.59, $P<0.0001$) and ovarian cancer (43 obs. versus 1.52 exp.; SMR 28.38, $P<0.0001$), as well as stomach cancer (4 obs. versus 0.77 exp.; SMR 5.16, $P=0.008$) and rectal cancer (3 obs. versus 0.73 exp.; SMR 4.12, $P=0.038$). These tumour types all remained significantly increased when the index cases are excluded from the analyses (Table 3). Among men (Table 4), there was a non-significant increase in the incidence of all cancers (25 obs. versus 22.87 exp; SMR 1.09, $P=0.401$). However, among the individual tumour types, there was a significant increase in invasive skin cancer (invasive squamous cell carcinomas, median age at diagnosis 82 years) (5 obs. versus 0.83 exp.; SMR 6.02, $P=0.002$). Analysing both sexes together did not reveal additional tumour types with increased risk (Table 5). Among spouses (data not shown), there was no significant increase in cancer overall or among individual tumour types.

BRCA2

In all, 100 malignant tumours occurred among the 728 relatives (383 males and 345 females) belonging to the *BRCA2* associated families. The tumours occurred in 42

Table 4. *Tumour incidence among* 549 *males (*12 713.7 *person-years) belonging to* BRCA1*-associated families*

ICD-7	Type	Obs.	Exp.	SMR	95% CI	*P* value
140–209	All malignant tumours	25	22.87	1.09	0.71–1.61	0.401
151	Stomach	2	1.40	1.43	0.17–5.15	0.409
153	Large bowel	2	1.55	1.29	0.16–4.65	0.671
154	Rectum	1	1.04	0.96	0.02–5.36	0.96
155	Gallbladder	1	0.24	4.14	0.10–23.08	0.214
157	Pancreas	1	0.76	1.32	0.03–7.34	0.532
162	Lung	4	2.17	1.84	0.5–4.72	0.175
177	Prostate	5	4.28	1.17	0.38–2.72	0.626
181	Urinary bladder	1	1.46	0.68	0.02–3.81	1.0
191	Skin	5	0.83	6.02	1.96–14.05	0.002
201	Hodgkin's disease	1	0.30	3.29	0.08–18.34	0.262
204	Acute leukaemia	1	0.53	1.88	0.05–10.50	0.412
204.1	Chronic lymphatic leukaemia	1	0.25	4.08	0.10–22.74	0.217

Note: Only ICD sites for tumors found among. *BRCA1* associated family members are shown. Obs., observed number of cases; Exp., expected number of cases; SMR, standardised morbidity ratio; CI, confidence interval.

Table 5. *Tumour incidence among* 1145 *individuals (*27 075.3 *person-years) belonging to* BRCA1*-associated families (*1086 *individuals or* 25 385.1 *after exclusion of the index cases)*

		All					Index excluded				
ICD-7	Type	Obs.	Exp.	SMR	95% CI	*P* value	Obs.	Exp.	SMR	95% CI	*P* value
140–209	All malignant tumours	150	46.62	3.22	2.72–3.78	<0.0001	86	43.33	1.98	1.59–2.45	<0.0001
151	Stomach	6	2.18	2.76	1.01–6.00	0.024	6	2.08	2.88	1.06–6.27	0.020
153	Large bowel	3	3.08	0.98	0.20–2.85	1.0	3	2.89	1.04	0.21–3.04	0.768
154	Rectum	4	1.77	2.26	0.62–5.79	0.21	4	1.68	2.38	0.65–6.10	0.180
155	Gallbladder	1	0.67	1.49	0.04–8.30	0.489	1	0.62	1.61	0.04–8.99	0.462
157	Pancreas	3	1.32	2.28	0.47–6.65	0.147	3	1.25	2.40	0.49–7.01	0.132
162	Lung	6	2.90	2.07	0.76–4.51	0.074	6	2.80	2.15	0.79–4.67	0.064
170	Breast	60	6.30	9.53	7.27–12.27	<0.0001	20	5.36	3.73	2.28–5.76	<0.0001
172	Uterine body	1	1.39	0.72	0.02–4.00	1.0	0	1.19			
175	Ovary	43	1.52	28.38	20.54–38.23	<0.0001	20	1.29	15.49	9.46–23.92	<0.0001
176	Vulva	1	0.19	5.39	0.14–30.00	0.1695	1	0.16	6.18	0.16–34.45	0.149
177	Prostate	5	4.28	1.17	0.38–2.72	0.626	5	4.28	1.17	0.38–2.72	0.626
181	Urinary bladder	1	1.92	0.52	0.01–2.90	1.0	1	1.86	0.54	0.01–2.99	1.0
190	Melanoma	2	1.63	1.23	0.15–4.43	0.681	2	1.49	1.34	0.16–4.85	0.664
191	Skin	6	1.25	4.78	1.75–10.41	0.002	6	1.20	5.01	1.84–10.90	0.001
193	CNS	1	2.26	0.44	0.01–2.46	0.734	1	2.11	0.47	0.01–2.64	0.730
201	Hodgkin's disease	1	0.52	1.91	0.05–10.66	0.407	1	0.49	2.03	0.05–11.33	0.388
204	Acute leukaemia	1	0.99	1.01	0.03–5.62	0.629	1	0.95	1.05	0.03–5.85	0.614
204	Chronic lymphatic leukaemia	1	0.36	2.79	0.07–15.56	0.301	1	0.35	2.90	0.07–16.14	0.292

Note: Only ICD sites for tumours found among *BRCA1* associated family members are shown. Obs., observed number of cases; Exp., expected number of cases; SMR, standardised morbidity ratio; CI, confidence interval; CNS, central nervous system.

men and 55 women, of whom 38 men and 49 women had a single tumour, 4 men and 5 women had two tumours 1 women had four separate tumours. Of the 100 tumours, 87 were available for analyses. Excluded were six tumours not identified in the Central Cancer Registry, two tumours (a stomach and a pancreatic cancer) diagnosed as the third and fourth tumour of a woman previously affected by bilateral breast cancer and, finally, five tumours diagnosed prior to 1958 or after 1995.

Apart from breast cancer, only a limited number of tumour types occurred more than once in individual families and none more than twice. These tumours were prostate and cervical cancer in family 119, ovarian cancer in family 175 and 304, melanoma in family 46 and urinary bladder cancer in family 296 (two tumours in the same individual). The occurrence of ovarian cancer was not restricted to the ovarian cancer cluster region (OCCR) in exon 11 of the *BRCA2* gene. In Tables 6–8 observed versus expected cancer cases are represented and the calculated SMR values shown. For women belonging to *BRCA2*-associated families (Table 6), there was a significant excess of all cancers (55 obs. versus 19.06 exp.; SMR 2.89, $P<0.0001$). With regard to individual

Table 6. *Tumour incidence among* 345 *women (*8472.8 *person-years) belonging to* BRCA2*-associated families (*318 *women or* 7710.5 *person-years when index cases were excluded)*

		All					Index excluded				
ICD-7	Type	Obs.	Exp.	SMR	95% CI	*P* value	Obs.	Exp.	SMR	95% CI	*P* value
140–209	All malignant tumours	55	19.06	2.89	2.17–3.76	<0.0001	32	16.97	1.89	1.29–2.66	0.0009
150	Oesophagus	1	0.09	11.01	0.28–61.34	0.087	1	0.08	11.91	0.30–66.37	0.081
151	Stomach	1	0.73	1.37	0.03–7.64	0.518	1	0.68	1.48	0.04–8.24	0.491
152	Duodenum	1	0.08	13.29	0.34–74.06	0.072	1	0.07	14.29	0.4–82.5	0.065
153	Large bowel	2	1.35	1.48	0.18–5.34	0.391	2	1.23	1.63	0.20–5.89	0.347
157	Pancreas	1	0.52	1.93	0.05–10.73	0.405	1	0.47	2.12	0.05–11.79	0.377
162	Lung	1	0.62	1.61	0.04–8.97	0.463	1	0.55	1.82	0.05–10.15	0.423
170	Breast	29	4.90	5.91	3.96–8.49	<0.0001	13	4.29	3.03	1.61–5.18	0.0005
171	Cervix	4	0.95	4.21	1.15–10.79	0.016	3	0.82	3.65	0.75–10.66	0.051
172	Uterine body	1	1.13	0.89	0.02–4.94	1.0	1	0.99	1.01	0.03–5.63	0.628
175	Ovary	6	1.16	5.16	1.89–11.24	0.001	1	1.02	0.98	0.02–5.47	1.0
176	Vulva	1	0.16	6.09	0.15–33.91	0.152	1	0.15	6.73	0.17–37.50	0.138
180	Renal	1	0.51	1.97	0.05–10.96	0.399	1	0.46	2.19	0.06–12.18	0.367
190	Melanoma	2	0.62	3.21	0.39–11.60	0.129	1	0.54	1.84	0.05–10.24	0.419
200	Non-Hodgkin's lymphoma	1	0.45	2.22	0.06–12.38	0.362	1	0.40	2.49	0.06–13.88	0.331

Note: Only ICD sites for tumours found among *BRCA2*-associated family members are shown. Obs., observed number of cases; Exp., expected number of cases; SMR, standardised morbidity ratio; CI, confidence interval.

Table 7. *Tumour incidence among* 383 *males (*8300.7 *person-years) belonging to* BRCA2*-associated families (*366 *or* 8075.3 *person-years when index excluded)*

		All					Index excluded				
ICD-7	Type	Obs.	Exp.	SMR	95% CI	*P* value	Obs.	Exp.	SMR	95% CI	*P* value
140-209	All malignant tumours	32	15.94	2.01	1.37–2.83	<0.0001	25	14.97	1.67	1.08–2.47	0.014
141	Oral cavity	1	0.13	7.46	0.19–41.55	0.125	1	0.12	8.05	0.20–44.85	0.117
151	Stomach	2	1.11	1.79	0.22–6.48	0.306	2	1.07	1.88	0.23–6.78	0.288
153	Large bowel	1	1.10	0.91	0.02–5.06	1.0	1	1.03	0.97	0.02–5.38	1.0
154	Rectum	1	0.74	1.35	0.03–7.53	0.523	1	0.69	1.44	0.04–8.05	0.499
162	Lung	2	1.41	1.42	0.17–5.11	0.412	2	1.30	1.53	0.19–5.54	0.375
163	Pleura	1	0.07	13.76	0.35–76.69	0.070	1	0.08	14.7	0.4–81.6	0.066
170	Breast	8	0.03	290.52	125.42–572.43	<0.0001	0	0.03			
177	Prostate	7	3.16	2.21	0.89–4.56	0.042	7	2.97	2.36	0.95–4.86	0.032
181	Urinary bladder	2	0.97	2.06	0.25–7.43	0.254	2	0.90	2.22	0.27–8.03	0.227
190	Melanoma	1	0.48	2.07	0.05–11.51	0.383	1	0.45	2.23	0.06–12.42	0.361
192	Retinoblastoma	1	0.06	16.64	0.41–89.94	0.060	1	0.06	3.0	0.4–93.6	0.058
193	CNS	2	0.70	2.88	0.35–10.39	0.154	2	0.66	3.04	0.37–10.96	0.142
200	Non-Hodgkin's lymphoma	1	0.51	1.94	0.05–10.83	0.402	1	0.48	2.08	0.05–11.61	0.381
203	Multiple myeloma	1	0.22	4.51	0.11–25.15	0.199	1	0.21	4.84	0.12–26.99	0.187
204	Acute leukaemia	1	0.35	2.84	0.07–15.83	0.297	1	0.34	2.93	0.07–16.32	0.289

Note: Only ICD sites for tumours found among *BRCA2* associated family members are shown. Obs., observed number of cases; Exp., expected number of cases; SMR, standardised morbidity ratio; CI, confidence interval; CNS, central nervous system.

tumour types, there was a significant increase in breast cancer (29 obs. versus 4.9 exp.; SMR 5.91, $P<0.0001$), ovarian cancer (6 obs. versus 1.16 exp.; SMR 5.16, $P=0.001$) and cervical cancer (4 obs. versus 0.95 exp.; SMR 4.21, $P=0.0016$). After exclusion of the index cases SMR remained significantly increased only for all tumours and breast cancer (Table 6). For males (Table 7), there was an overall excess of all tumours (32 obs. versus 15.94 exp.; SMR 2.01, $P<0.0001$). With regard to individual tumours, only breast cancer was significantly increased (8 obs. versus 0.03 exp.; SMR 290.52, $P<0.0001$). After exclusion of the index cases, this excess disappeared. The incidence of prostate

Table 8. *Tumour incidence among* 728 *individuals (*16 773.5 *person-years) belonging to* BRCA2*-associated families (*684 *individuals or* 15 785.8 *person-year after exclusion of the index cases)*

		All					Index excluded				
ICD-7	Type	Obs.	Exp.	SMR	95%CI	*P* value	Obs.	Exp.	SMR	95% CI	*P* value
140–209	All malignant tumours	87	35	2.49	1.99–3.07	<0.0001	57	31.92	1.79	1.35–2.31	<0.0001
141	Oral cavity	1	0.24	4.17	0.11–23.26	0.213	1	0.22	4.55	0.12–25.34	0.197
150	Oesophagus	1	0.28	3.58	0.09–19.93	0.244	1	0.26	3.85	0.10–21.45	0.229
151	Stomach	3	1.84	1.63	0.34–4.75	0.439	3	1.74	1.72	0.36–5.04	0.254
152	Duodenum	1	0.16	6.31	0.16–35.18	0.146	1	0.14	6.90	0.2–38.6	0.134
153	Large bowel	3	2.45	1.22	0.25–3.57	0.741	3	2.26	1.33	0.27–3.88	0.497
154	Rectum	1	1.38	0.72	0.02–4.03	1.0	1	1.27	0.79	0.02–4.38	1.0
157	Pancreas	1	1.05	0.95	0.02–5.32	1.0	1	0.97	1.03	0.03–5.76	0.620
162	Lung	3	2.03	1.48	0.30–4.31	0.463	3	1.85	1.62	0.33–4.73	0.440
163	Pleura	1	0.12	8.21	0.21–45.73	0.115	1	0.11	8.9	0.2–49.5	0.106
170	Breast	37	4.93	7.50	5.28–10.34	<0.0001	14	4.32	3.24	1.77–5.44	0.0002
171	Cervix	4	0.95	4.21	1.15–10.79	0.016	3	0.82	3.65	0.75–10.66	0.051
172	Uterine body	1	1.13	0.89	0.02–4.94	1.0	1	0.99	1.01	0.03–5.63	0.628
175	Ovary	6	1.16	5.16	1.89–11.23	0.001	1	1.02	0.98	0.02–5.47	1.0
176	Vulva	1	0.16	6.09	0.15–33.91	0.152	1	0.15	6.73	0.17–37.50	0.138
177	Prostate	7	3.16	2.21	0.89–4.56	0.042	7	2.97	2.36	0.95–4.86	0.032
180	Renal	1	1.14	0.88	0.02–4.88	1.0	1	1.05	0.96	0.02–5.33	1.0
181	Urinary bladder	2	1.38	1.45	0.18–5.24	0.401	2	1.27	1.58	0.19–5.70	0.362
192	Retinoblastoma	1	0.12	8.28	0.21–46.15	0.114	1	0.11	8.9	0.2–49.5	0.1065
190	Melanoma	2	1.11	2.71	0.56–7.92	0.101	2	0.99	2.01	0.24–7.28	0.262
193	CNS	2	1.53	1.31	0.16–4.73	0.668	2	1.40	1.42	0.17–5.15	0.409
200	Non-Hodgkin's lymphoma	2	0.96	2.07	0.25–7.49	0.251	2	0.88	2.27	0.27–8.20	0.221
203	Multiple melanoma	1	0.42	2.36	0.06–13.15	0.345	1	0.39	2.58	0.07–14.36	0.322
204	Acute leukemia	1	0.65	1.54	0.04–8.59	0.477	1	0.62	1.62	0.04–9.03	0.460

Note: Only ICD sites for tumours found among *BRCA2*-associated family members are shown. Obs., observed number of cases; Exp., expected number of cases; SMR, standardised morbidity ratio; CI, confidence interval; CNS, central nervous system.

cancer was borderline significantly high (7 obs. versus 3.16 exp.; SMR 2.21, CI = 0.89–4.56; $P = 0.042$), more so when the index cases were excluded (7 obs. versus 2.97 exp.; SMR 2.36, CI = 0.95–4.86; $P = 0.032$). Analysing both sexes together did not reveal additional tumour types with increased risk (Table 8). There is no significant increase of any tumour type in the spouses overall or for individual tumour types (data not shown).

DISCUSSION

For south Swedish *BRCA1* and *BRCA2* families, only a limited number of cancer types occurred in excess of that expected. Thus for *BRCA1*, it was not unexpected that the incidence of breast and ovarian cancer would be greatly increased. The study supports the fact that an increased risk exists for these tumour types, after the exclusion of the index cases for women belonging to *BRCA1*-associated families, as well as female breast cancer in *BRCA2*-associated families, as has been suggested by previous studies on high risk families [2, 7, 10, 13, 15–17].

However, in the *BRCA1* families, the reported excess of colon and prostate cancer was not observed [2]. It must be stressed that though our study was small, it is of similar size to that of Ford and associates [2] and we believe that if any major excess risk for these tumour types existed, we would have seen indications thereof. As both stomach and, to a lesser degree, rectal cancers had increased SMR values, we cannot exclude that there may exist a small increment in risk for gastrointestinal tumours, at least among females. These observations are based on a limited number of tumours. Until further studies are available, we believe it to be doubtful whether individuals belonging to *BRCA1* families should be informed of a possible increased risk for gastrointestinal tumours and thus be subjected to a possibly unnecessary, expensive surveillance and increased psychosocial burden. Furthermore, from our review of the clinical and pathological records it now appears that the classification of some of the stomach cancers may be erroneous. Some may have been primary ovarian cancers, rather than stomach cancers with metastases to the ovaries. It is interesting that four of these tumours occurred in families sharing the same germline mutation (2594delC) for which the risk of ovarian cancer appears greater than that for breast cancer (15 cases versus 10). The median and mean ages of the four cases of stomach cancer that occurred in women in *BRCA1*-related families were 72 and 71.4 years, respectively. The risk of male breast cancer has been reported as increased with *BRCA1* mutations [1]. Not a single case was observed in our *BRCA1*-associated families suggesting that the risk increment, if true, is low. However, the sample of male breast cancer cases, from which *BRCA2* mutation carriers were included in the study, was not screened for *BRCA1* mutations. With regard to the increased frequency of skin cancer observed in the males, these were non-fatal cancers diagnosed late in life. No childhood tumour was found. In conclusion, tumour predisposition in *BRCA1*-associated families appears to be restricted to adult females with an increased incidence of breast and ovarian cancer, and to a far lesser degree stomach cancer and rectal cancers in females, as well as skin cancer in males. Thus, we believe, that currently, surveillance of family members belonging to *BRCA1* families should focus on the two organs that the present and past studies have found excessive incidences of cancer in, i.e. the breast and ovaries.

The situation is more complex for *BRCA2*. Only a limited number of studies have tried to assess the risk for cancer types other than breast and ovarian cancers [5–7, 9–14]. Similarly to observations made in those studies, we found the risk of cancer to vary greatly between individual families. Whereas breast cancer was the dominating tumour type in the majority of families, there were some families where a large number of different tumours occurred (Family 46 with cases of colon, lung, breast cancer (4), malignant melanoma (2) and retinoblastoma; and family 119 with cases of head and neck cancer, gastrointestinal cancers—stomach and duodenum, cancers of prostate, cervix, breast (3), kidney, lymphoma and glioma), supporting observations that *BRCA2* may in some cases predispose to a multitude of different tumours [6, 7, 11, 13, 14].

Perhaps more interestingly, it appears that the incidence of cancer differs by the sex of the proband. In the 7 families with a male breast cancer proband (families 131, 292–297), only a single female breast cancer was found [21]. Conversely, there was not a single male breast cancer case in any of the families of female probands. This observation may be spurious, as we know of two cases of male cancer in family 91 in relatives of a female proband. These males belong to a Danish branch of the family not included in the study. Nevertheless, in male proband families, 19 of the 25 tumours occurred in males, whilst in female proband families, 63 of 77 tumours occurred in females. This might be due to the influence of the proposed *BRCA2* modifying factors [1]. 6 of the 7 male proband families were identified from a study of a population-based tumour collection [21], whereas 11 of the 14 of the female proband families where identified by family history, suggesting that the tumour incidence may reflect tumour incidence in population-based non-high risk families, as suggested by recent studies on Ashkenazi Jews [17], rather than a gender specific modifying factor. A similar 'lack' of tumours among female relatives of male breast cancer patients has however been noted in Icelandic *BRCA2* families [11].

Whilst the incidence of ovarian cancer was clearly increased in *BRCA2*-associated families when the index cases were included, this was not so when they were excluded. This may reflect a selection bias and indicate that the risk of ovarian cancer was less than previously proposed. Nevertheless, we do not believe that surveillance for ovarian cancer is unnecessary in *BRCA2*-associated families, though it may be proposed that the role of or need for prophylactic operations may be less than in *BRCA1*-associated families. As is the case for *BRCA1*, we suspect that ovarian cancer may occur outside the ovaries proper in *BRCA2* germline mutation carriers. In family 10 a case of peritoneal carcinomatosis occurred in a woman aged 70 years, that in the pathological report was judged to be ovarian-like cancer derived from the peritoneum. To our knowledge, no such cases have previously been reported in a *BRCA2*-associated family.

The increased incidence of pancreatic cancer reported in some studies [10–13] was not observed in this study. As pancreatic cancer is also a tumour type where germline and somatic mutations of *BRCA2* have been reported [9], this is puzzling. It may be that there was a lack of an internal or external modifying risk factor that prevents the increased risk observed in other studies, or, conversely, there was perhaps an early onset diagnosis of other fatal tumours preventing the subsequent onset of pancreatic cancer occurring. A case in family 10 could support this hypothesis. In this family, a woman, diagnosed with bilateral, non-fatal breast cancer at

the age of 71 years and 75 years as well as a simultaneous gastric carcinoma at 75 years, was diagnosed at post mortem at the age of 76 years with a fourth malignant tumour, a pancreatic cancer. As only the first two tumours of an individual were included in the statistical study, these cases were not included in the risk estimations. Furthermore, in family 304, a case of peritoneal cancer occurred in 1 individual at the age of 66 years that was coded as a tumour of unknown origin (ICD-7 199) in the cancer registry. Review of the tumour and pathological records suggest that this was most likely a pancreatic cancer. For these reasons it cannot be ruled out that there was an underestimation of the risk for pancreatic cancer in the *BRCA2*-families in this study.

An increased frequency of laryngeal cancer reported in at least one study [13] was not seen in this study. However, prostate and cervical cancer were frequent, as has been described previously [6, 7, 10, 11, 13]. No case of ocular melanoma was observed. A single childhood tumour, a unilateral retinoblastoma, occurred. In conclusion, the incidence of breast cancer and, to a lesser degree, ovarian cancer and cervical cancer was increased in adult women belonging to *BRCA2*-associated families, whilst among adult men prostate cancer was frequent.

The use of expanded pedigrees without mutation testing of individuals from all branches can be questioned. It obviously can lead to an overestimation of incidence of breast and ovarian cancer when a branch of a family is selected because of the prevalence of these malignancies. In the majority of families the choice of family branch was obvious based on verified mutations of relatives or the pattern in the pedigree. In some cases, the situation was less obvious. Here we chose to exclude both branches in the *BRCA1*-related cases. On the contrary, we included both branches in the *BRCA2*-related cases were the index case was male breast cancer. We did so because, in the *BRCA1*-related cases, these problems occurred in early branches of the families leaving a significant number of relatives with a close relation to the proband. In the *BRCA2*-related families this approach would leave us with only relatives in the same and younger generations as the proband, and thus a risk for underestimation of recurrent non breast- or ovarian tumour types among relatives in preceding generations.

Sporadic cases are included in this study along with hereditary ones, since only a minority of the patients with tumours were tested for *BRCA1* or *BRCA2* mutations. It should be pointed out that the study is limited in that no subdivision into carriers and non-carriers was performed and, therefore, gene penetrance data cannot be estimated. The great majority of the study groups are still young. Therefore, it is likely that changes in the tumour spectra will occur upon follow-up of this group, barring the effects of any major preventative effort. It is possible that some of the subtypes of cancers observed may have preferentially occurred among carriers of a mutated gene, yet have been obscured by a low/normal rate among non-carriers. No studies to our knowledge have shown a divergence from chance allocation of being a carrier or non-carrier of a *BRCA1*/*BRCA2* mutation among the offspring of a mutation-carrier. Considering the rates observed it is thus unlikely, even if all cases of a certain subtype occurred in mutation-carriers, that the risk of cancers other than for breast and ovarian cancer are of importance for clinical follow-up. An exception may be the observation of four out of six *BRCA1* stomach cancers being associated with the same germline mutation, though this awaits verification in additional families and after gene mutation analysis.

In conclusion, whilst other tumour types may occur in *BRCA1*- and *BRCA2*-associated families, our study does not detect any clinically obvious significantly increased risks for tumours other than breast and ovarian cancer among women in families with germline mutations in *BRCA1* or *BRCA2*. In our opinion it may, therefore, be appropriate to restrict clinical follow-up and surveillance in these families to the increased risk for these cancers.

1. Ford D, Easton DF, Stratton M, *et al.* Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. *Am J Hum Genet* 1998, **62**, 676–689.
2. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Consortium BCL. Risks of cancer in *BRCA1*-mutation carriers. *Lancet* 1994, **343**, 692–695.
3. Arason A, Barkadóttir RB, Egilsson V. Linkage analysis of chromosome 17q markers and breast-ovarian cancer in Iclandic families, and possible relationship to prostatic cancer. *Am J Hum Genet* 1993, **52**, 711–717.
4. Burke W, Petersen G, Lynch P, *et al.* Recommendations for follow-up care of individuals with an inherited predisposition to cancer. *JAMA* 1997, **227**, 915–919.
5. Goldgar DE, Neuhausen SL, Steele L, *et al.* A 45-year follow-up of kindred 107 and the search for *BRCA2*. *J Natl Cancer Inst Monogr* 1995, **17**, 15–19.
6. Gudmundsson J, Johannesdottir G, Bergthorsson JT, *et al.* Different tumor types from *BRCA2* carriers show wild-type chromosome deletion on 13q12-q13. *Cancer Res* 1995, **55**, 4830–4832.
7. Tonin P, Ghadirian P, Phelan C, *et al.* A large multisitic cancer family linked to *BRCA2*. *J Med Genet* 1995, **32**, 982–984.
8. Katagiri T, Nakamura Y, Miki Y. Mutations in the *BRCA2* gene in hepatocellular carcinomas. *Cancer Res* 1996, **56**, 4475–4557.
9. Goggins M, Schutte M, Lu J, *et al.* Germline *BRCA2* gene mutations in patients with apparently sporadic pancreatic carcinomas. *Cancer Res* 1996, **56**, 5360–5364.
10. Tonin P, Weber B, Offit K, *et al.* Frequency of recurrent *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish breast cancer families. *Nature Med* 1996, **2**, 1179–1183.
11. Thorlacius S, Olafsdottir G, Jonasson L, *et al.* A single *BRCA2* mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. *Nat Genet* 1996, **13**, 117–119.
12. Phelan CM, Lancaster JM, Tonin P, *et al.* Mutation analysis of the *BRCA2* gene in 49 sitespecific breast cancer families. *Nat Genet* 1996, **13**, 120–122.
13. Easton DF, Steele L, Fields P, *et al.* Cancer risks in two large breast cancer families linked to *BRCA2* on chromosome 13q12-13. *Am J Hum Genet* 1997, **61**, 120–128.
14. Nelson NJ. *BRCA1/2* carriers. *J Natl Cancer Inst* 1998, **90**, 189–190.
15. Easton DF, Bishop DT, Ford D, Crockford GP. Consortium BCL. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1993, **52**, 678–701.
16. Easton DF, Ford D, Bishop DT. Consortium BCL. Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. *Am J Hum Genet* 1995, **56**, 265–271.
17. Struewing JP, Hartge P, Wacholder S, *et al.* The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* 1997, **336**, 1401–1408.
18. Friedman LS, Szabo CI, Ostermeyer EA, *et al.* Novel inherited mutations and variable expressivity of *BRCA1* alleles, including the founder mutation 185del AG in Ashkenazi Jewish families. *Am J Hum Genet* 1995, **57**, 1284–1297.
19. Stoppa-Lyonnet D, Fricker JP, Essioux L, *et al.* Segregation of two *BRCA1* mutations in a single family. *Am J Hum Genet* 1996, **59**, 479–481.
20. Liede A, Tonin PN, Sun CC, *et al.* Is hereditary site-specific ovarian cancer a distinct genetic condition? *Am J Med Genet* 1998, **75**, 55–58.

21. Haraldsson K, Loman N, Johannsson O, Olsson H, Borg Å. *BRCA2* germline mutations are frequent in male breast cancer patients without a family history of the disease. *Cancer Res* 1998, **58**, 1367–1371.
22. Johannsson OT, Idvall I, Anderson C, Borg Å, Egilsson V, Olsson H. Tumour biological features of *BRCA1*-induced breast and ovarian cancer. *Eur J Cancer* 1997, **33**, 362–371.
23. Håkansson S, Johannsson O, Johansson U, *et al.* Moderate frequency of *BRCA1* and *BRCA2* germ-line mutation in Scandinavian familial breast cancer. *Am J Hum Genet* 1997, **60**, 1068–1078.

Acknowledgements—Financial support for this study was provided by grants from the Swedish Cancer Society; CTRF Foundation, Stockholm; Mrs Bertha Kamprad Foundation; Medical Faculty of Lund University, Lund; Gunnar, Arvid and Elisabeth Nilsson Foundation, Helsingborg, Sweden; and the Nordic Cancer Union, Copenhagen, Denmark.