Familial Cancer (2007) 6:121–129
DOI 10.1007/s10689-006-9113-9

ORIGINAL PAPER

The interval between cancer diagnosis among mothers and offspring in a population-based cohort

Ora Paltiel · Yehiel Friedlander · Lisa Deutsch · Rebecca Yanetz · Ronit Calderon-Margalit · Efrat Tiram · Hagit Hochner · Micha Barchana · Susan Harlap · Orly Manor

Received: 3 October 2006 / Accepted: 7 December 2006 / Published online: 11 January 2007

Abstract
Background Familial cancers may be due to shared genes or environment, or chance aggregation. We explored the possibility that ascertainment bias influences cancer detection in families, bearing upon the time interval between diagnosis of affected mothers and offspring.
Methods The Jerusalem Perinatal Study (JPS) comprises all mothers (n = 39,734) from Western Jerusalem who gave birth 1964 –1976 and their offspring (n = 88,829). After linking identification numbers with Israel's Cancer Registry we measured the absolute time interval between initial cancer diagnoses in affected mother-offspring pairs. We tested the probability of obtaining intervals as short as those observed by chance alone, using a permutation test on the median interval.
Results By June 2003 cancer had developed in 105 mother-offspring pairs within the cohort. Common sites among mothers were breast (47%), colorectal (9%), non-Hodgkin lymphoma (NHL) (8%) and cervix (7%), while for offspring in affected pairs common cancers were leukemia (12.4%), thyroid (13.3%), NHL (10.5%), breast (10.5%) and melanoma (7.6%). The median interval between diagnoses was 5.9 years, but for 33% of affected pairs the interval was ≤3 years. The probability of this occurring by chance alone was 0.03. This held true whether the offspring's or mother's diagnosis was first ($P < 0.01$).
Conclusions In a population-based cohort followed for three decades, the absolute interval between the diagnosis of cancer in mothers and their offspring is shorter than expected by chance. Explanations include shared environmental exposures or the possibility that cancer ascertainment in one pair member affects health behaviors in the other resulting in early diagnosis. The latter may bias the estimation of anticipation and survival in familial cancers.

Keywords Hereditary cancer · Time to diagnosis · Ascertainment bias · Cohort study

Supported by Grant RO1-CA-80197 from the National Institutes of Health (NIH)

O. Paltiel · Y. Friedlander · L. Deutsch · R. Yanetz · R. Calderon-Margalit · E. Tiram · H. Hochner · O. Manor
Braun School of Public Health, Hadassah-Hebrew University, 12272, Jerusalem 91120, Israel

M. Barchana
Israel Cancer Registry, Ministry of Health, Jerusalem, Israel

S. Harlap
Mailman School of Public Health, Columbia University, New York, NY 10032, USA

O. Paltiel (✉)
School of Public Health, P.O. Box 12000, Jerusalem 91220, Israel
e-mail: ora@vms.huji.ac.il

Introduction

Cancers occurring in first degree relatives of cancer patients may be due to rare highly penetrant genetic syndromes (reviewed in [1]), more frequent low-penetrance genetic variants, shared environment [2], or chance occurrences within a family. Cancers occurring in carriers of the mutations in cancer-predisposing genes such as BRCA1 and 2, TP53, APC, mismatch

repair genes and others are often characterized by a younger age at onset than sporadic cancers [1]. Often these syndromes are typified by tumors at different sites among family members (such as sarcoma in children and breast cancer in mothers in the Li-Fraumeni syndrome), rather than identical sites [3]. Evidence of ''anticipation'', that is, younger age at onset or more aggressive disease in successive generations has been observed in hematologic malignancies [4–6] and has been suggested in hereditary colon [7] and breast cancer [8]. Despite the fact that a biological explanation for anticipation has been developed [9] controversies remain regarding the extent and validity of this phenomenon [10, 11]. The estimation of anticipation is determined by the time interval between cancer diagnoses in subsequent generations.

It is estimated that only 5–10% of cancers in the population are due to hereditary single gene mutations [1]. Thus many cancers occurring among multiple family members are multifactorial in origin and may be attributed to gene-environment interactions [12], environmental exposures or shared polygenic inheritance. Stiller has proposed that the excess cancer risk observed in first degree family members of children diagnosed with cancer is due to known hereditary syndromes [13]. However, studies in large population-based registries report only modestly elevated overall excess risks for maternal cancers in families where a child has experienced childhood cancer, with standardized incidence ratios (SIRs) of 1–1.1 [14, 15]. Cancers at specific sites, such as retinoblastoma, sarcomas and lymphomas have been found to be elevated in parents of affected children [15]. When the risk for children with affected mothers is assessed, increased relative risks have been observed for those whose mothers were diagnosed with breast, gynecological , thyroid, endocrine, hematopoietic and nervous system cancers [16]. Cancers at concordant sites are associated with high SIRs within families [17–19].

The time interval between the diagnosis of mothers and offspring with cancer has not been the subject of intensive investigation. Familial cancers which do not occur at similar ages, but rather are closely spaced in calendar time suggest a shared environmental exposure in susceptible family members [20], or health behaviors which promote the diagnosis of clinically silent cancers or both.

We examined patterns of diagnosis of cancer within mother-offspring pairs in a population-based cohort, the Jerusalem Perinatal Study (JPS), in order to obtain clues to the contribution of biological and behavioral factors to the timing of detection of familial cancers.

Methods

Study population

The Jerusalem Perinatal Study is a database containing information on all births to residents of Western Jerusalem between 1964 and 1976. The study was initially established for research on pre-eclampsia and was later expanded to include other pregnancy complications and birth outcomes. Details of the study cohort have been previously published [21, 22]. Briefly, the database consists of 42,957 mothers and 91,459 live-born offspring. Information regarding ethnicity (including mother's father's (maternal grandfather's) place of birth), socioeconomic status graded into six categories by father's occupation, and years of education are available on virtually all mothers. Information on all offspring includes birth weight, birth order, type of delivery and singleton vs multiple birth. Information on maternal health and obstetric characteristics is available on 95% of the traced mothers. Smoking status (ever/never) is known for 54% of the mothers. The median age of living mothers in the cohort at last follow-up was 59 years (June 2004) while that of the offspring was 33 years.

Data Linkage

In Israel all residents have a unique identity number. Using this number we linked the JPS file with the Israel Population Registry, tracing vital status on 39,734 (92.5%) mothers and 90,078 (98.5%) offspring in January 2004. We then linked this file to the Israel Cancer Registry, updating cancer incidence in the cohort to June 30, 2003. The Cancer Registry has existed since 1960 and notification of all malignant tumors (except non-melanoma skin cancer), as well as benign brain tumors, has been obligatory by law since 1981. Even before that, registration for most tumor sites was considered >90% complete [23]. This study focuses on the mother-offspring pairs in which both received a diagnosis of cancer.

Statistical methods

We examined the frequencies of sociodemographic characteristics in the affected mother-offspring pairs, comparing them with the entire JPS cohort. Mother's education was recorded as the maximal number of years noted in any birth in the cohort. Mother's age and father's age were assessed for the first birth in the cohort. We then compared cancer types, which occurred in the pairs with those ascertained among

cohort members who did not have an affected child or mother according to ICD-O topography and morphology codes [24]. For several cancers we calculated age-standardized morbidity ratios comparing the observed numbers of cancers with those expected given the age distribution of the entire cohort. 95% confidence intervals were calculated for these ratios.

We estimated the correlation between the age at diagnosis of cancer for the mother and the offspring as well as year of diagnosis in the pairs. We examined the time interval, in absolute terms, between the mothers' and offsprings' cancer diagnoses in terms of mean and median. We then performed a permutation test to examine the probability of occurrence of time intervals as short as or shorter than those observed in our cohort occurring by chance alone (one-sided test). The permutation test was based on randomly matching pairs of mothers and offspring and computing the median of the time interval elapsed between the diagnosis of the first and second pair members. For every configuration 50×10^4 permutations were generated. We then obtained the *P* value by counting the percentage of permutations in which the median was smaller or equal to that observed. All permutations were programmed using the C language.

We examined these permutations in different subgroups: occurrence of mother's cancer first or second, mother with breast cancer or other cancer, mother's age at cancer diagnosis <50 years or ≥50 years, and offspring's age at cancer diagnosis <15 years or 15+ years. We repeated the analysis excluding non-invasive cancers (such as in-situ carcinoma of the cervix) where the diagnosis is more likely to have been influenced by ascertainment bias. Out of concern that short follow-up may cause artefacts in the assessment of the time interval between cancer detection across generations, we also analyzed pairs in which the offspring were born in the 1960s and 1970s separately.

As an additional procedure to determine the probability of obtaining the observed median survival by chance alone we examined the occurrence of cancer in offspring and mother within the entire cohort using random combinations as follows: from the entire cohort of mothers and children diagnosed with cancer we excluded those cases where both mothers and offspring were affected, yielding 3684 mothers and 785 offspring with cancer. From this subgroup of non-familial cancers we randomly created 100 hypothetical pairs of mothers and offspring and calculated the absolute time interval elapsed between the diagnoses of the generated pair members. We repeated this procedure 1,000 times and determined the P value by calculating the proportion of replications in which the median was shorter than that observed.

Finally for mother-offspring pairs with mother's cancer occurring first, we fitted a Cox proportional hazards model to the time to diagnosis of offspring, starting at the time of mother's diagnosis and adjusting for offspring age. We then plotted the estimated survival function at the mean offspring age. In a similar way we have plotted the estimated survival function for mother's time to diagnosis among pairs with offspring cancer occurring first.

The study received ethical approval from the Institutional Review Boards of the Hadassah University Hospital and Columbia University.

Results

There were 3784 mothers and 890 offspring in the JPS cohort who were reported to the cancer registry with a diagnosis of a first primary cancer until June 2003. Of these, 105 were mother-offspring pairs. Five mothers had two offspring with cancer and each was treated as an independent event. The demographic characteristics of mothers are shown in Table 1. Compared to women in the entire cohort, women with cancer were more likely to be of Western (European, North and South American, Australian) origin, and had a higher mean age at first birth. Women who had cancer and had a child with cancer were less likely to be of high socioeconomic status, more likely to be educated beyond 12 years and less likely to be uniparous, smokers, or to have given birth to a male child as their firstborn in the cohort compared with women with cancer and no affected offspring in the cohort.

The tumor characteristics of mother and offspring cancer pairs are shown in Table 2. The most prevalent types of cancer in mothers without an affected child were breast (41.8%), colon and rectum (9%), melanoma (5.8%) and thyroid (4.9%), whereas the most common diagnoses of mothers in mother-offspring cancer pairs were breast (47%), colon (9%), non-Hodgkin lymphoma (NHL) (8 %) and cervical cancer (7%). Non-Hodgkin lymphomas (observed/expected 2.2, 95% confidence interval 1.1–4.3) were significantly over-represented in mothers with affected offspring. As for the offspring, the most prevalent sites for those in the cohort without an affected mother were Hodgkin Disease (12.2%), leukemia (8.7%), breast cancer (8.8%), NHL (7.5%), cervical cancer (7.6%), brain (6%) and melanoma (6.4%), whereas in the mother-offspring pairs thyroid tumors (13.3%), leukemia (12.4%), breast cancers (10.5%) and NHL (10.5%)

Table 1 Sociodemographic characteristics of mothers in the cohort and mothers with cancer

Variable	Entire cohort (n = 39,734)	%	Women in the cohort with cancer (n = 3,784)	%	Women with cancer whose offspring had cancer (n = 100)	%
Birthplace of mother						
Israel	18,362	46.2	1,796	47.5	50	50
Other	21,372	53.8	1,988	52.5	50	50
Mother's father's birthplace						
Israel	5,401	13.6	520	13.7	11	11
West (Europe, America etc.)	14,098	35.5	1,532	40.5	45	45
North Africa	8,480	21.3	685	18.1	16	16
Western Asia	11,164	28.1	1,020	27	28	28
Religion						
Jewish	39,129	98.5	3,755	99.2	100	100
Other	605	1.5	29	0.8		
Socioeconomic Status (based on father's occupation)						
1–2 High	13,998	35.2	1,344	35.5	28	28
3–4	15,545	39.2	1,513	40	47	47
5–6 Low	10,191	25.6	927	24.5	25	25
Education						
0–8 year	11,069	28.7	1,068	29.1	26	26
9–12 year	14,047	36.9	1,306	34.5	36	36
13+ years	12,833	32.3	1,294	34.2	38	38
Missing		3		3.1		
Mean age at first birth (SD)	26.3 (5.7)		28.1 (5.9)		27.0 (5.1)	
Sibship size in cohort						
1	15,576	39.2	1,519	40.1	16	16
1‘2–3	18,650	47	1,816	48	63	63
4–5	4,400	11.1	367	9.7	18	18
6+	1,108	2.8	82	2.2	3	3
Father's mean age at first birth (SD)	33.0 (7.2)		34.6 (7.1)		31.7 (6.5)	
Gender of first child						
Male	20,601	51.8	2,003	52.9	45	45
Female	19,133	48.2	1,781	47.1	55	55
Smoking						
Ever	8,688	39	732	37.6	18	29
Never	13,563	61	1,214	62.4	44	71

were most common. Rare childhood tumors such as medulloblastoma (observed/expected 5.9, 95% confidence interval 1.6–15.11) were over-represented in the children whose mothers also had cancer, whereas Hodgkin Disease (observed/expected = 0.39, 95% confidence interval 0.13–0.9) was significantly under-represented. The mean and median age of cancer diagnosis for all mothers in the cohort was 52 years, similar to that of mothers with an affected offspring. Likewise, the corresponding ages for offspring with cancer in the entire cohort were similar to those with an affected mother (mean 22.6 and 22.7 years respectively).

Breast cancer in the mother was co-observed with the same tumor in a daughter in seven families. Other concordant sites were lymphoma in three pairs, melanoma and colorectal cancers in two pairs each, and thyroid cancer in one pair. The combination of sarcoma and breast cancer occurred in four pairs, suggesting the Li- Fraumeni syndrome. There were no cases of the combination of endometrial and colon cancer in pairs. Thyroid cancer in the offspring was associated with breast cancer in the mother in six cases.

The interval between cancer diagnosis in the first and second pair members was evaluable in 103 pairs in which the date of diagnosis of both members was documented. The correlation between the child's and mother's age at diagnosis was moderate in the pairs (r = 0.199, r^2 = 0.04, P = 0.042), while the correlation between calendar year of diagnosis among the pairs was

Table 2 Tumor characteristics of mothers and offspring with and without affected family members

	Mothers without affected offspring (n = 3684)	Mothers with affected offspring n = 100	Offspring without affected mothers(n = 785)	Offspring with affected mother (n = 105)
Cancer site	*n (%)*	*n* &%	*n* (%)	*n* (%)
Breast	1539 (41.8)	47	69 (8.9)	11 (10.5)
Colon/Rectum	332 (9)	9	12 (1.5)	3 (2.9)
Ovary	136 (3.7)	1	19 (2.4)	–
Uterus	146 (4)	2	6 (0.8)	2 (1.9)
Melanoma	212 (5.8)	3	50 (6.3)	8 (7.6)
Lung	103 (2.8)	3	4 (0.5)	–
Thyroid	180 (4.9)	4	66 (8.4)	14 (13.3)
Cervix	150 (4.1)	7	60 (7.6)	7 (6.7)
Non-Hodgkin Lymphoma	137 (3.7)	8	59 (7.5)	11 (10.5)
Leukemia	53 (1.4)	–	68 (8.7)	13 (12.4)
Hodgkin Disease	35 (1.0)	2	96(12.2)	5 (4.8)
Brain	49 (1.3)	–	55 (7)	4 (3.8)
Stomach	64 (1.7)	4	5 (0.6)	–
Pancreas	50 (1.4)	–	1 (0.1)	–
Kidney	47 (1.3)	1	5 (0.6)	–
Bladder	47 (1.3)	–	7 (0.9)	–
Sarcoma	68 (1.8)	4	39 (5)	7 (6.7)
Liver/ biliary tract	32 (0.9)	2	1 (0.1)	–
Head and neck	66 (1.7)	–	12 (1.5)	2 (1.9)
Unknown primary	70 (1.9)	–	7 (0.9)	1 (1)
Testis	–	–	50 (6.4)	4 (3.8)
Retinoblastoma	–	–	6 (0.8)	1 (1.0)
Neuroblastoma	–	–	8 (1)	3 (2.9)
Nephroblastoma	–	–	4 (0.5)	1 (1.0)
Medulloblastoma	–	–	5 (0.6)	4 (3.8)
Other	169 (4.5)	1	72 (9,2)	4 (3.8)
% Males	–	–	44.4	43.8
Age at diagnosis Mean (SD)	51.7 [10.6]	52 [10]	22.6 [9.6]	22.7 [9.8]
Median	52	52	24.5	24.8
0–4			75 (8.4)	10 (9.5)
5–14	2 (0.1)		95 (10.7)	11 (10.5)
15–29	11 (4.3)	1	502 (56.4)	60 (57.1)
30–44	809 (21.4)	25	216 (24.3)	24 (22.9)
45–59	2029 (53.6)	51	–	
60+	826 (21.8)	23	–	
Missing	4 (0.1)		2 (0.2)	

weaker (r = 0.175, r^2 = 0.03, P = 0.07). The mean and median time between cancer discovery in one member of a mother-child pair and the second member were relatively short, that is 8.6 and 5.9 years respectively (Table 3). The probability of an interval this short or shorter occurring by chance is 0.03. The findings were similar whether the mother's or child's diagnosis came first, however the median was shorter in the latter.

The median interval was particularly short (4.7 years) in the subgroup of offspring diagnosed as adolescents and young adults ≥15 years of age. The finding was not observed when only mothers with breast cancer were considered. Those pairs in which the offspring was born in the 1960s showed a shorter median interval (5.9 years) compared with those born in the 1970s (median 6.3 years).

Restricting our analysis to invasive cancers (ie excluding 13 cases of in situ tumours) yielded a similar overall median and P value (0.02). When we based our calculations on the entire cohort of mothers and offspring diagnosed with cancer generating hypothetical pairs, our results were similar, with only 49 of 1000 replications yielding medians as short or shorter than the observed median. Moreover the lower quartile observed among the 103 pairs in our study was 2.1 years, whereas in only 15 of 1000 replications in the whole cohort the lower quartile was as short or shorter than the observed.

Figures 1 and 2 show the time to cancer detection (based on a Cox proportional hazards model adjusted for age) after proband detection in children of affected mothers and in mothers of affected children, respec-

Table 3 Absolute Interval between diagnoses of malignancies in affected mother and offspring pairs

Interval	All pairs	Mother diagnosed first	Offspring diagnosed first	Mother with breast cancer	Mother other cancer	Mother <50 years of age at diagnosis	Mother ≥50 years of age at diagnosis	Offspring diagnosed <15 years of age	Offspring diagnosed ≥15years of age	Child DOB < 1970	Child DOB ≥1970
n	103	46	57	48	55	42	61	21	82	57	46
% ≤3 yearrs	33	30	35	29	36	26	38	14	38	32	35
Mean years	8.6	8.7	8.5	8.6	8.6	10.3	7.4	15.2	6.9	8.6	8.5
SD	8.2	8.3	8.2	7.4	8.9	8.7	7.7	9.1	7.1	8.3	8.2
Median years	5.9	6.4	5.9	7.3	5.2	8.1	5.1	15.2	4.7	5.9	6.3
P value	0.03	0.0067	0.0015	>0.1	0.06	0.075	>0.1	>0.1	0.026	0.026	>0.1

P value, for a permutation test on the median

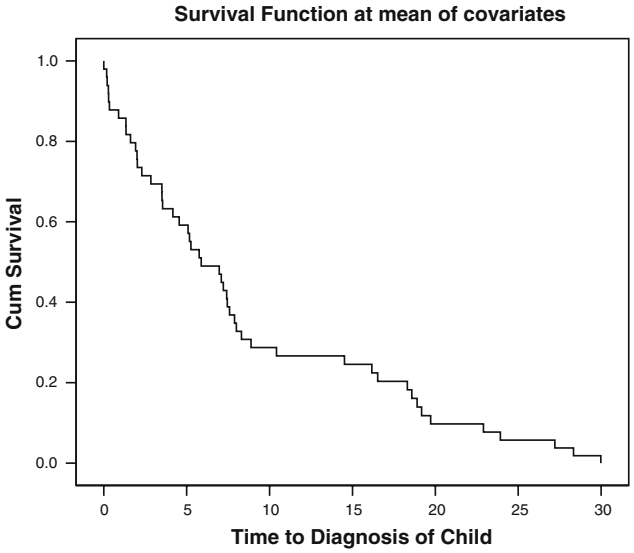

Fig. 1 Cox Model for time to offspring's diagnosis of cancer. X-axis; Years from mother's diagnosis Y-axis: Percent not diagnosed

tively. In both instances we observed a 50% probability that cancers detected among pair members would be diagnosed within five years of the proband's diagnosis.

We specifically examined the 34 (33%) cases in which both members of the pairs were diagnosed within 3 years of each other (Table 4) We found that in 18 (53%) the offspring was diagnosed first, both diagnoses occurred in the same month in 2 (6%) and the mother's diagnosis came first in 14 (41%) pairs. In six (18%) of these cases cancer sites were concordant. Breast cancers in the mother represented 42% of

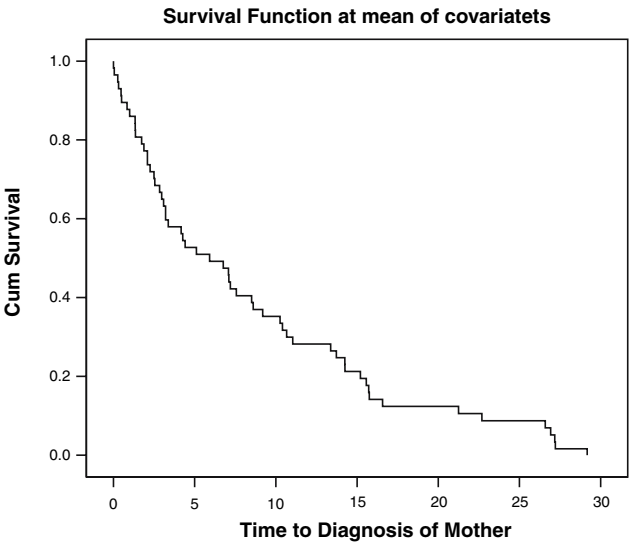

Fig. 2 Cox model for time to mother's diagnosis of cancer. X-axis: Years from offspring's diagnosis Y-axis: Percent not diagnosed

Table 4 Year, age and site of tumors in pairs diagnosed within 3 years of each other

Interval between offspring's and mother's diagnosis	Year of diagnosis		Age at diagnosis		Cancer site/type	
	Offspring	Mother	Offspring	Mother	Offspring	Mother
25–36 months	1989	1992	26	60	Hodgkin	Breast
offspring first $n = 5$	1999	2002	32	66	Cervix in situ	Colon
	1998	2000	33	69	Thyroid	Lung
	1988	1990	22	49	Melanoma	Melanoma
	1999	2002	31	58	Breast	Osteosarcoma
13–24 months	1970	1972	5	40	NHL	Breast
offspring first $n = 7$	1997	1999	28	60	NHL	Breast
	2000	2002	30	62	Osteosarcoma	Cutaneous NHL
	1993	1995	20	56	NHL	Breast
	1997	1999	31	55	Breast	Colon
	1996	1997	20	60	NHL	Breast
	1971	1972	7	42	AML	Breast
0–12 months $n = 13$	2002	2002	34	57	NHL	Breast
	2002	2003	33	67	Breast	Lung
	2001	2002	31	68	Unknown 1	NHL
	1993	1993	24	45	Rectum	Colon
	2002	2002	29	67	Breast	Breast
	1990	1990	17	46	Soft tissue sarcoma	Cervix in situ
	1991	1990	16	49	Sarcoma	Breast
	1996	1997	28	50	Thyroid	Breast
	2000	2000	29	53	Breast	Breast
	2002	2002	31	55	ALL	Cervix in situ
	1995	1995	23	50	Hodgkin	Uterus
	2000	2000	25	51	AML	Colon
	2002	2002	36	65	Sinus	Breast
13–24 months mother	1997	1996	26	60	Thyroid	Thyroid
first $n = 5$	2000	1998	33	58	Brain	Cervix
	1994	1992	28	57	Colon	Breast
	1998	1996	27	46	Thyroid	Breast
	1988	1986	11	45	Osteosarcoma	Uterus
25–36 months mother	1993	1991	24	46	Astrocytoma (brain)	Stomach
first $n = 4$	1997	1995	24	55	Melanoma in situ	Melanoma
	1998	1995	24	47	Oral sqamous Cell	Lung
	1994	1991	27	60	NHL	NHL
Total $n = 34$						

cancers in this subgroup, similar to their proportion in the cohort, whereas in the offspring, breast cancers were somewhat over-represented, comprising 15% of tumors in the group. All cancers but two (one case of NHL and one of lung cancer) detected in mothers within one year of their offspring could have been detected by early diagnosis procedures (breast, colon, cervix-in situ, and uterus). On the other hand, when the offspring was diagnosed soon after the mother the cancer sites included sarcomas, lymphoma and brain cancer which are less likely to be subject to over-diagnosis or lead time bias.

Discussion

In our study population we were able to discern several families which could be suspected (but not confirmed, due to the limited extent of the pedigrees) and lack of analysis of the appropriate genes to have hereditary cancer syndromes such as Li-Fraumeni syndrome, hereditary breast cancer, FAP, or familial melanoma. Apart from these we observed a relatively large number of families in which the offspring was diagnosed with non-medullary thyroid cancer and the mother suffered from a variety of tumors.

Family studies of cancer have been fraught with bias, such as biased ascertainment of more severely affected family members or biased participation rates among family members with a higher perceived risk of cancer [25]. Studies based on cancer registries are generally thought to largely mitigate these biases. In this study, neither the mothers nor the offspring have been followed up sufficiently in order to ascertain all potential cases of familial cancer. Furthermore to our

knowledge none of the mothers in the cohort were survivors of childhood cancer although three were diagnosed before the birth of their affected offspring. The short follow-up (maximum 40 years) in the offspring could spuriously result in a false inference of anticipation in these families. In our cohort, however, pairs followed-up from the 1960's had a shorter interval than those followed from the 1970's rendering this artefact unlikely. Other causes of spurious anticipation have included cohort effects [10], secular trends in earlier exposures to carcinogens such as cigarette smoking [26], curtailment of fertility in women with early onset hereditary breast cancer [27], gene-environment interactions such as obesity and lack of physical activity in younger generations of BRCA mutation carriers [28], or methodologic issues such as use of mean ages at cancer diagnosis instead of life table approaches [11].

In this study, the striking finding is the temporal proximity of the diagnosis of mothers and offspring. One third of the pairs were diagnosed within three years of each other, mainly at discordant sites. This clustering in time may suggest common exposures to carcinogenic factors, as was suggested by Grossman in a study of familial brain cancer [20]. Furthermore, inheritance of low penetrance modifying genes by the offspring may contribute to the short interval between diagnoses.

Alternatively or additionally, the large proportion of tumors in this group which are detectable by screening techniques suggests that health behaviors in one of the members of the pair may have been modified by the detection of cancer in the other pair member. Bermejo and Hemminki [29] have recently reported results from the Swedish Family Cancer database which corroborate our findings. They found that daughters of women with breast cancer and melanoma were particularly likely to have these tumors detected within a year of the mother's diagnosis. This suggests that lead time bias may operate preferentially in families where one family member has already been diagnosed with cancer. We do not have data on stages of cancer at the time of detection, but removing the few in-situ cancers from our analysis did not substantially alter the results. While daughters of breast cancer patients have been found to have greater feelings of vulnerability to breast cancer there are no differences in their mammography practices compared to women without a maternal history [30]. Older women with a family history of breast cancer have not been found to be compliant with recommendations for yearly mammography screening [31], however the short-term response to having had a family member diagnosed with cancer is not known and may vary among populations. Most studies have focused on coping strategies of mothers with young children or adolescents with cancer [32] and not on their health behaviors. In our study, most of the offspring from pairs in whom cancer was diagnosed within three years of their mother, were in their third or fourth decades of life. We are not aware of any published data regarding health behaviors, especially screening practices, among mothers of young adult cancer patients. Further follow up of this cohort, as well as an assessment of cancer detection among fathers will shed more light on the robustness of our findings.

In conclusion, there is an unexpectedly short time interval between the diagnosis of cancer among mothers and their young adult children in the Jerusalem Perinatal Study cohort. Apart from the obvious psychosocial implications for families coping with two generations with cancer in a short interval, this finding has implications for research exploring anticipation as well as survival in familial cancers. Furthermore, studies examining health behaviors of parents of young adult cancer patients are warranted.

References

1. Hemminki K, Li X (2004) Familial risk in testicular cancer as a clue to a heritable environmental aetiology. Br J Cancer 90:1765–1770
2. Nagy R, Sweet K, Eng C (2004) Highly penetrant hereditary cancer syndromes. Oncogene 23:6445–6470
3. Li FP, Fraumeni JF (1969) Rhabdomyosarcoma in children: epidemiologic study and identification of a familial cancer syndrome. J Natl Cancer Inst 43:1365–1373
4. Wiernik PH, Ashwin M, Hu X et al (2001) Anticipation in familial chronic lymphocytic leukemia. Brit J Haematol 113:407–414
5. Shugart YY, Hemminki K, Vaittinen P et al (2001) Apparent anticipation and heterogeneous transmission patterns in familial Hodgkin's and non-Hodgkin's Lymphoma: report from a study based on Swedish cancer database. Leuk Lymphoma 42:407–415
6. Wiernik PH, Wang SQ, Hu X et al (2000) Age of onset evidence for anticipation in familial non-Hodgkin's lymphoma. Brit J Haematol 108:72–79
7. Rodriguez-Bigas MA, Lee PH, O'Malley L et al (1996) Establishment of a hereditary nonpolyposis colorectal cancer registry. Dis Colon Rectum 39:649–653
8. Dagan E, Gershoni-Baruch R (2002) Anticipation in hereditary breast cancer. Clin Genet 62:147–150
9. Harper PS, Harley HG, Reardon W et al (1992) Anticipation in myotonic dystrophy: new light on an old problem. Am J Hum Genet 51:10–16
10. Tsai YY, Petersen GM, Booker SV et al (1997) Evidence against genetic anticipation in familial colorectal cancer. Genet Epidemiology 14:435–446
11. Goldin LR, Pfeiffer RM, Li X et al (2004) Familial risk of lymphoproliferative tumors in families of patients with

chronic lymphocytic leukemia: results from the Swedish Family-Cancer Database. Blood 104:1850–1854
12. Vineis P (2004) Individual susceptibility to carcinogens. Oncogene 23:6477–6483
13. Stiller CA (2004) Epidemiology and genetics of childhood cancer. Oncogene 23:6429–6444
14. Olsen JH, Boice JD, Seersholm N et al (1995) Cancer in the parents of children with cancer. N Engl J Med 333:1594–1599
15. Pang D, McNally R, Kelsey A et al (2003) Cancer incidence and mortality among the parents of a population-based series of 2604 children with cancer. Cancer Epidemiol Biomarkers Prev 12:538–544
16. Hemminki K, Vaittinen P (1997) Effect of paternal and maternal cancer on cancer in the offspring: a population-based study. Cancer Epidemiol Biomarkers Prev 6:993–997
17. Hemminki K, Li X, Plna K et al (2001) The Nation-wide Swedish Family-Cancer Database. Acta Onc 40:772–777
18. Dong C, Hemminki K (2001) Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. Int J Cancer 92:144–150
19. Hemminki K, Mutanen P (2001) Parental cancer as a risk factor for nine common childhood malignancies. Br J Cancer 84:990–993
20. Grossman SA, Osman M, Hruban R et al (1999) Central nervous system cancers in first-degree relatives and spouses. Cancer Invest 17:299–308
21. Harlap S, Davies AM, Grover NB et al (1977) The Jerusalem perinatal study: the first decade 1964–73. Isr J Med Sci 13:1073–1091
22. Davies AM, Prywes R, Tzur B et al (1969) The Jerusalem perinatal study. 1. Design and organization of a continuing, community-based, record linked survey. Isr J Med Sci 5:1095–1106
23. Steinitz R, Parkin DM, Young JL, et al. Cancer incidence in Jewish migrants to Israel, 1961–1981. (1989) In Steinitz R, Parkin DM, Young JL, Bieber CA, Katz L (eds) Vol 98. IARC Sci Publ, pp 6–7
24. International classification of disease for oncology: morphology of neoplasms (2000) 3rd edn
25. Watson P, Lynch HT (2001) Cancer risk in mismatch repair gene mutation carriers. Familial Cancer 1:57–60
26. Lynch HT (2000) Anticipation in familial Hodgkin's lymphoma. Hum Genet 107:290–293
27. Hoh J, Heitjan DF, Merette C et al (2001) Ascertainment and anticipation in family studies. Hum Hered 51:23–26
28. King M, Marks JH, (2003) Mandell JB for the New York Breast Cancer Study Group Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302:643–645
29. Bermejo JL, Hemminki K (2005) Familial risk of cancer shortly after diagnosis of the first familial tumor. JNCI 97:1575–9
30. Wellisch DK, Gritz ER, Schain W et al (1991) Psychological functioning of daughters of breast cancer patients. Part I: Daughters and comparison subjects. Psychosomatics 32:324–336
31. Lerman C, Daly M, Sands C et al (1993) Mammography adherence and psychological distress among women at risk for breast cancer. J Natl Cancer Inst 85:1074–1080
32. Grootenhuis MA, Last BF (1997) Adjustment and coping by parents of children with cancer: a review of the literature. Support Care Cancer 5:466–484