Differences in the characteristics of families with *BRCA1* and *BRCA2* mutations in Israel

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Three specific mutations in the *BRCA1* (185delAG, 5382insC) and *BRCA2* (6174delT) genes have been reported to be of high prevalence in the Jewish Ashkenazi population. We studied the differences in phenotype of families carrying these mutations. All consecutive families found by the CHS Familial Cancer Service to carry one of the three 'Jewish' mutations of the *BRCA1/BRCA2* genes were evaluated for phenotypic characteristics. Chi-squared and Student's *t*-test statistics were employed to study differences in a variety of clinical and demographic parameters. A total of 111 families with 1499 family members were included. Among them 454 cases of cancer (297 in breast/ovary) were reported. Ovarian cancer, but not breast cancer, was detected at a significantly younger age among carriers of 185delT compared with other mutation carriers. In families with 185delAG, 5382insC and 6174delT mutations, breast cancer was found in 20.2, 39.4 and 24.1% of all identified women (born between 1900 and 1975), correspondingly. The corresponding figures for ovarian cancer were 13.9, 6.8 and 4.9%. Families carrying the 5382insC mutation had the highest probability of expressing bilateral breast cancer (38.9% of families, 15.4% of women with cancer, 6.1% of all women in family) and metachronous breast and ovary tumours (22.2, 9.8 and 4.5% correspondingly). Other tumours were reported in 7.9, 9.1 and 12.0% of women and 9.5, 12.9 and 15.8% of men in families with 185delAG, 5382insC, 6174delT, correspondingly. Marked phenotypic differences were found between families carrying different BRCA mutations warranting mutation-specific counselling to families seeking risk-reduction advice. 5382insC emerged as a most aggressive mutation. *European Journal of Cancer Prevention* 14:357–361 © 2005 Lippincott Williams & Wilkins.

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Introduction

Breast cancer is a leading cause of cancer incidence as well as cancer mortality in Israel as well as in many other western countries (Israel Cancer Registry, 1997; Parkin *et al.*, 1999). In Israel close to 4000 women are diagnosed with breast cancer annually (Rennert, 1999a). Of all women diagnosed with breast cancer in Israel more than 95% are Jewish. A significant variation in incidence rates is evident between Jews of Ashkenazi origin (born in Europe–America, 101/100 000) and Jews of Sepharadi origin (born in Africa, 60/100 000 and Asia 61/100 000) (Israel Cancer Registry, 1997). New immigrants from Russia express higher breast cancer rates than those who immigrated 20 and more years ago (Rennert, 1999b).

Two major genes have thus far been demonstrated to be related to breast (and ovarian) cancer occurrence, *BRCA1* and *BRCA2*. The *BRCA1* gene was identified and reported by several groups in 1994 (Miki *et al.*, 1994; Simard *et al.*, 1994). Two of the mutations in this gene, 185delAG (Tonin *et al.*, 1995) and 5382insC (Szabo and King, 1997), were reported to be exceptionally common in Ashkenazi Jewish women. *BRCA2* was identified in 1995 (Wooster *et al.*, 1995) and its mutation in 6174delT was also found to be of high prevalence, especially in Jewish women (Tonin *et al.*, 1996). All together it is estimated that some 2.5% of Ashkenazi Jewish women carry one of these three founding mutations (Struewing *et al.*, 1995; Oddoux *et al.*, 1996). Of the Ashkenazi Jewish women with breast cancer, almost 12% carry a mutation in one of these genes and among those with family history of breast and ovary cancer this rate rises to 45% (Tonin *et al.*, 1996). A study was designed to evaluate differences in the demographic and clinical characteristics of Jewish families carrying the various mutations.

Patients and methods

All families approaching the CHS National Familial Cancer Consultation Service who were found to carry one of the three Jewish Ashkenazi mutations in the BRCA genes were included in this analysis. The service provides open access to the general public and also receives referrals from oncology centres and primary care physicians. Commonly, probands described the occurrence of several cancer cases in the family but many times a young age at diagnosis of cancer was the sole indication for testing. All families were studied through the service;

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pedigrees were drawn including all family members up to at least two generations higher than the proband's generation. Bloods were collected from as many family members as possible. An IRB-approved consent form was signed by all family members receiving counselling by the service. Tumour blocks were sought when possible and analysed if necessary to determine the positivity of a family. One single family member with a mutation was enough to define the family as positive and no effort was made thereafter to show that all cancer patients in the family carried the gene. All reported family members born between 1900 and 1975 were counted to serve as a denominator for calculation of the proportion affected. In the rare case when it was not possible to determine which branch of the pedigree (paternal or maternal) was the source of the genetic disorder, both sides were included in the denominator and their cancers in the numerators. Several families had the same mutation originate from both the maternal and the paternal sides of the family, and some had different mutations appearing in the different family branches.

Numerator and denominator data were handled in a way to include only the relevant pedigree information for each of the mutations. This analysis concentrated on the differences in age at diagnosis, country of origin (studying the origin of the oldest available generation of the family), mean number of tumours in the family, and the occurrence of bilateral breast cancer or breast and ovarian cancers in the same patient. Age at diagnosis was missing in 13 women with breast cancer and in six women with ovarian cancer (6.4% of cases). In eight of these cases, age at death was available. In these cases the age of diagnosis was artificially set as one year before the age of death. Exact year of birth was missing for 19 women with cancer and birth-cohort assignment in these cases was according to birth-year of siblings and children.

Statistical analysis included the calculation of two-tailed ANOVA and Kruskal–Wallis non-parametric test for differences between the three mutations in the means of continuous variables (such as age, number of cases) and the chi-squared test for differences in non-continuous variables (such as origin), with a significance level set at $P \leq 0.05$.

Results

All together 111 families, most of them of Ashkenazi origin, have thus far been studied with at least one known carrier of the specific mutations 185delAG or 5382insC in *BRCA1* and 6174delT in *BRCA2*. A few more families were detected with other mutations in the BRCA genes, which are not discussed in this paper.

In the 111 carrier families, 1499 relevant family members born between 1900 and 1975 have been identified (861 women and 638 men) and among them 454 cancers were reported, 297 breast or ovary cancers in women, 79 other tumours in women and 76 tumours in men. Of the 'other tumours' group, 11 tumours in women were described by the family members as abdominal or metastatic tumours, suggestive but not confirmed to be of ovarian or peritoneal origin due to lack of documentation.

Of the positive families, 61 (55.0%) carried the 185delAG mutation, 18 (16.2%) carried the 5382insC mutation and 32 (28.8%) carried the 6174delT *BRCA2* mutation.

Age at diagnosis

The mean age at diagnosis of breast cancer in the carriers of the two *BRCA1* mutations (185delAG, 5382insC) and the 6174delT *BRCA2* mutation were similar (46.6, 46.2 and 48.2 years correspondingly, no statistically significant difference). Mean age at detection of ovarian cancer was much younger among the carriers of *BRCA1* 185delAG mutations (52.4 years) than in the carriers of the 5382insC (60.8 years) and 6174delT (60.7 years) mutations ($P = 0.005$).

Origin

Significant differences in origin of the families by mutation type were found. 185delAG in *BRCA1* was most common among families of Romanian (54.2% of all Romanian families) and Polish origin (61.3% of families) and more rare among families of Russian origin (41.7%). The 5382insC mutation in *BRCA1* was most common among Russian families (37.5% of all Russian families) and rare in families of Polish origin (9.7%). The 6174delT mutation in *BRCA2* was much more balanced, yet more common in Polish (29.0%) and Romanian families (29.2%) then in other Ashkenazi origins. The latter was the only mutation identified in families identifying themselves as non-Ashkenazi of the Balkan area (Bulgaria, Greece, and Turkey) in our series.

Cumulative incidence of breast and ovarian tumours

Breast cancer was reported in 20.2% of all women, born between 1900 and 1975, in families in which the *BRCA1* 185delAG mutation was detected. A similar incidence, 24.1%, was noted among women belonging to families carrying the *BRCA2* 6174delT mutation. In families carrying the *BRCA1* 5382insC mutation, a much higher incidence of 39.4% was noted. This is despite a similar mean age of the women in the mutation-specific pedigrees. The assumption that all reported breast and ovarian cancers in these families are actually in mutation carriers was found plausible. In our database 104 women with breast or ovary cancers were actually tested for existence of the mutation. All tested women with cancer, except for one from a family carrying the 5382insC mutation, were found to be carriers. Ovarian cancer was found in 13.9% of eligible women from families carrying

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the *BRCA1* 185delAG mutation as compared with only 6.8% of women in families carrying of *BRCA1* 5382insC mutation and 4.9% of women in families carrying *BRCA2* 6174delT (Table 1).

Mean number of malignancies

Families carrying the different mutations differed in the proportion of women affected with breast and ovary malignancies. In families with 185delAG *BRCA1* mutation, a mean of 1.67 women were affected by breast cancer and a mean of 1.13 women were affected by ovarian cancer (Table 2). The mean number of breast malignancies was similar for families carrying the *BRCA2* 6174delT mutation (1.69), but much higher for families carrying the 5382insC mutation (2.89). Ovarian cancer was less common in families carrying the 5382insC and the 6174delT mutations (0.50 and 0.34 correspondingly).

Multiple primary breast and ovary cancers

Bilateral breast cancer in at least one family member was expressed much more frequently in families carrying the 185delAG (29.5%). and the 5382insC (38.9%) mutations than in the families carrying the 6174delT *BRCA2* (9.4%). Women with metachronous cancers of the breast and ovary were also reported more frequently in families carrying the 185delAG (19.7%) and the 5382insC (22.2%) mutations, but in only one family with the 6174delT *BRCA2* mutation (3.1%). Women in *BRCA1*-positive families had a 3–4.5 times higher risk of bilateral breast cancer and 6–11 times higher risk of breast and ovarian cancer in the same woman than women from *BRCA2*-positive families. Almost 20% of all women with the 185delAG mutation developed bilateral breast tumours and 7–10% of all *BRCA1* mutation carriers with cancer developed combined breast and ovary cancers. Both phenomena were significantly less frequent among the *BRCA2* mutation carriers (Table 2).

Frequency of tumours other than in the breast and ovary

The proportion of women having tumours other than in the breast or the ovary was 7.9% in the families with 185delAG, 9.1% in families with 5382insC and 12.0% in families with 6174delT.

All together men in these families carried a significantly lower risk of any cancer than did the women. The proportion of men having any tumours was 9.5% in the families with 185delAG, 12.9% in families with 5382insC and 15.9% in families with 6174delT. Of the 76 tumours in men, 16 were diagnosed before the age of 50 (2.5% in 185delAG, 1% in 5382insC, and 3.3% in 6174delT).

The most common non-breast–ovary tumours detected in women of this group were 10 abdominal NOS tumours, eight uterine tumours, eight colorectal tumours, five leukaemia, four lung tumours and four pancreatic tumours. In men colorectal cancer was the most frequent (nine cases), followed by lung cancer (seven cases), stomach cancer (six cases), pancreatic cancer (five cases), central nervous system (five cases), leukaemia, liver,

Table 1 **Proportion (and 95% confidence intervals) of affected women in families carrying the three 'Jewish' *BRCA1* and *BRCA2* mutations**

Mutation type	No. of women	Breast cancer		Ovarian cancer	
		No. of women with cancer	Proportion of all women with cancer	No. of women with cancer	Proportion of all women with cancer
185delAG	505	102	20.2% (16.7, 23.7)	69	13.9% (10.7, 16.7)
5382insC	132	52	39.4% (31.1, 47.7)	9	6.8% (2.5, 11.1)
6174delT	224	54	24.1% (18.5, 29.7)	11	4.9% (2.1, 7.7)

Table 2 **Characteristics of occurrence of breast and ovary cancers, by mutation type**

	185delAG	5382insC	6174delT	*P*-value
Mean number of tumours per family				
Breast cancer	1.67 (±1.15)	2.89 (±1.53)	1.69 (±1.33)	<0.001*
Ovarian cancer	1.13 (±1.23)	0.50 (±0.86)	0.34 (±0.60)	0.003*
Proportion of families with:				
Bilateral breast cancer	29.5%	38.9%	9.4%	0.04
Breast + ovary	19.7%	22.2%	3.1%	ns
Proportion of female family members with:				
Bilateral breast cancer	4.0%	6.1%	1.3%	0.05
Breast + ovary	2.4%	4.5%	0.4%	0.04
Proportion of female cases with:				
Bilateral breast cancer[a]	19.6%	15.4%	5.6%	0.06
Breast + ovary[b]	7.0%	9.8%	1.5%	0.01

*Controlling for number of women in the family.
[a]Out of all breast cancers.
[b]Out of all breast and/or ovarian cancers.

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prostate and kidney (four cases each). It was not possible to calculate the expected rate for any of these tumours in this series, but the order and magnitude of tumours do not seem to be different from those described for the general population in Israel.

Discussion

Information regarding the genetic origins of breast and ovarian cancers is growing and estimates as to the magnitude of their contribution to cancer incidence are constantly changing (Struewing *et al.*, 1997). While population-based studies are clearly the most suitable for evaluation of the true magnitude of gene mutations and related-disease frequency, most of the current data come from less normalized populations attending specialized consultation services. The CHS Familial Cancer Consultation Service in Israel is community-oriented and is open, free of charge, to the general population as well as to family physician referrals. Most probands entering the service do not have a cancer diagnosis at time of entry. Such a service has a better probability of providing more normalized, though not optimal, data. The study relies on family information reported by family members. In 77.5% of the families genetic testing was undertaken by more than one family member (mean 2.7) and thus family information was usually provided by more than one relevant family member. Pedigrees were re-evaluated at every meeting with the family members. Documentation was sought for each reported case; however, documentation was often not available as many of the tumours in older people were diagnosed outside of Israel, mostly in Eastern Europe. Recall bias, though estimated to be low, might have led to an underestimation of the frequency of tumours, hence of the true penetrance. Tumours of unclear nature, mainly in the abdomen, could have a similar effect and lead to an underestimate of the frequency of ovarian tumours.

Major differences between the phenotype of families carrying the various mutations were detected. The 5382insC emerged as an aggressive mutation type, carrying the highest cumulative incidence rates for breast cancer, and the highest proportion of families and family members with bilateral breast cancer and breast–ovary combination. It also carries a higher risk for other tumours in both men and women than does the more common 185delAG *BRCA1* mutation. While 185delAG has been widely described to imply a high risk of breast and ovarian cancer with a younger age at presentation, the penetrance rates for this mutation, as well as information about other mutations, are still unresolved. Our data lend support to the lower estimates of penetrance of this mutation type for breast cancer, closer to more recent estimates (Struewing *et al.*, 1997; Hopper *et al.*, 1999; Anglian Breast Cancer Study Group, 2000) and further from the earlier reports of high estimates of penetrance, possibly partially reflecting selected family series (Levy-Lahad *et al.*, 1997; Schubert *et al.*, 1997; Ford *et al.*, 1998; Warner *et al.*, 1999; Risch *et al.*, 2001). Incidence of ovarian cancer was found to have rates similar to one report (Anglian Breast Cancer Study Group, 2000) for *BRCA1*. The incidence of breast cancer among the 6174delT-positive families was lower than previously reported by most (Schubert *et al.*, 1997; Ford *et al.*, 1998; Anglian Breast Cancer Study Group, 2000) but not all (Warner *et al.*, 1999) studies. Incidence of ovarian cancer in BRCA families was found to be much lower than one earlier estimate (Ford *et al.*, 1998) and is in line with a report from Israel of higher ovarian cancer penetrance in *BRCA1* mutation carriers (Levy-Lahad *et al.*, 1997). Ovarian cancer in *BRCA2* families was expressed at an older age, similar to that formerly reported (Risch *et al.*, 2001). The cumulative incidence of breast cancer in the families carrying the 5382insC *BRCA1* mutation was found to be very high. No reports were found in the literature to refer directly to this mutation type.

These findings serve to help the counsellor in advising the carriers. Advice should be given according to mutation type and should rely on best-known estimates of penetrance. Overestimation of penetrance may lead more women to choose interventions that may not be warranted, while underestimation of the penetrance might prevent women from taking aggressive enough measures of potentially life-saving remedies. The timing of interventions will also be influenced by these results. Ovarian cancer in the 5382insC and 6147delT carriers developed exclusively after the age of 45 years. This is not true for women with 185delAG, therefore different recommendations are warranted regarding the timing of prophylactic oophorectomy for women with different carrier patterns. The overall late age of occurrence of ovarian cancer does warrant the recommendation for prophylactic surgery also to older women. Women with the 5382insC mutation should be informed about the special clinical presentation of this mutation, which may warrant a more aggressive prevention approach. Counselling women with BRCA mutations should be tailored according to the specific mutation found to increase probability of success in preventing disease.

References

Anglian Breast Cancer Study Group (2000). Prevalence and penetrance of *BRCA1* and *BRCA2* mutations in a population-based series of breast cancer cases. *Br J Cancer* **83**: 1301–1308.

Ford D, Easton DF, Stratton M, *et al.* (1998). Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* **62**: 676–689.

Hopper JL, Southey MC, Dite GS, *et al.* (1999). Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in *BRCA1* and *BRCA2*. Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* **8**: 741–747.

Israel Cancer Registry (1997). Ministry of Health, Israel, 2001, http://www.health.gov.il/icr/ [accessed May 2005].

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Levy-Lahad E, Catane R, Eisenberg S, *et al.* (1997). Founder *BRCA1* and *BRCA2* mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. *Am J Hum Genet* **60**: 1059–1067.

Miki Y, Swensen J, Shattuck-Eidens D, *et al.* (1994). A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science* **266**: 66–71.

Oddoux C, Struewing JP, Clayton CM, *et al.* (1996). The carrier frequency of the *BRCA2* 6174 delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nature Genet* **14**: 188–190.

Parkin DM, Pisani P, Ferlay J (1999). Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* **80**: 827–841.

Rennert G (1999a). *Breast Cancer Screening in Israel*. Report to the Director General, Israel: Ministry of Health.

Rennert G (1999b). *Breast Cancer in Israel – Ethnic Peculiarities, Influence of Immigration, and Screening*. Florence: International Epidemiology Association Meeting.

Risch HA, McLaughlin JR, Cole DE, *et al.* (2001). Prevalence and penetrance of germline *BRCA1* and *BRCA2* mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet* **68**: 700–710.

Schubert EL, Lee MK, Mefford HC, *et al.* (1997). *BRCA2* in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to *BRCA1* or *BRCA2*. *Am J Hum Genet* **60**: 1031–1040.

Simard J, Tonin P, Durocher F, *et al.* (1994). Common origins of *BRCA1* mutations in Canadian breast and ovarian cancer families. *Nature Genet* **8**: 392–398.

Struewing JP, Abeliovich D, Peretz T, *et al.* (1995). The carrier frequency of the *BRCA1* 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nature Genet* **11**: 189–200.

Struewing JP, Hartge P, Wacholder S, *et al.* (1997). The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* **336**: 1401–1408.

Szabo CI, King MC (1997). Population genetics of *BRCA1* and *BRCA2*. *Am J Hum Genet* **60**: 1013–1020.

Tonin P, Serova O, Lenoir G, *et al.* (1995). *BRCA1* mutations in Ashkenazi Jewish women. *Am J Hum Genet* **7**: 189.

Tonin P, Weber B, Offit K, *et al.* (1996). Frequency of recurrent *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish breast cancer families. *Nature Med* **11**: 1179–1183.

Warner E, Foulkes W, Goodwin P, *et al.* (1999). Prevalence and penetrance of *BRCA1* and *BRCA2* gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* **91**: 1241–1247.

Wooster R, Bignell G, Swift S, *et al.* (1995). Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* **378**: 789–792.

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