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Survival in Familial, *BRCA1*-associated, and *BRCA2*-associated Epithelial Ovarian Cancer[1]

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ABSTRACT

The natural history of hereditary and *BRCA1*- and *BRCA2*-associated epithelial ovarian cancer may differ from that of sporadic disease. The purpose of this study was to compare the clinical characteristics of *BRCA1*- and *BRCA2*-associated hereditary ovarian cancer, hereditary ovarian cancer with no identified *BRCA1/2* mutation, and ovarian cancer in population-based controls. *BRCA1* and *BRCA2* mutation testing was carried out on index cases from 119 families with site-specific epithelial ovarian cancer or breast-ovarian cancer. We estimated overall survival in 151 patients from 57 *BRCA1* and *BRCA2* mutation families and compared it with that in 119 patients from 62 families in which a *BRCA1/2* mutation was not identified. We compared clinical outcome and data on tumor histopathology, grade, and stage. We also compared survival in familial epithelial ovarian cancer, whether or not a mutation was identified, with that of an age-matched set of population control cases. Overall survival at 5 years was 21% (95% confidence interval, 14–28) in cases from *BRCA1* mutation families, 25% (8–42) in *BRCA2* mutation families, and 19% (12–26) in families with no identified mutation ($P = 0.91$). Survival in familial ovarian cancer cases as a whole was significantly worse than for population controls ($P = 0.005$). In the familial cases, we found no differences in histopathological type, grade, or stage according to mutation status. Compared to population control cases, mucinous tumors occurred less frequently in the familial cases (2 *versus* 12%, $P < 0.001$), and a greater proportion of the familial cases presented with advanced disease (83% stage III/IV *versus* 56%; $P = 0.001$). We have shown that survival in familial ovarian cancer cases is worse than that in sporadic cases, whether or not a *BRCA1/2* mutation was identified, perhaps reflecting a difference in biology analogous to that observed in breast cancer.

INTRODUCTION

The breast-ovarian cancer susceptibility genes *BRCA1* and *BRCA2* are thought to account for the majority of families affected with site-specific ovarian cancer or the breast and ovarian cancer syndrome. The clinical features of breast cancer associated with germline mutations in *BRCA1* have been well described. Histopathological studies of *BRCA1*-linked tumors have shown these to be characterized by lower diploidy, lower mean aneuploid DNA index, higher proliferation rates, and a high S-phase fraction (1–3), features that are generally associated with a poor prognosis. Despite these features, the relationship between mutation status and survival remains unclear.

The characteristics of familial and inherited epithelial ovarian cancer are less well described. In one small study of site-specific familial ovarian cancer, no difference in grade was found between familial and sporadic ovarian tumors (4). Another study of familial ovarian cancer found a significantly higher proportion of serous cystadenocarcinoma in familial cases (83%) compared to controls (49%; Ref. 5). A high proportion of serous adenocarcinoma has also been reported for *BRCA1*-associated ovarian tumors (3, 6).

Several studies have investigated the outcome for patients with familial and *BRCA1*-associated ovarian cancer, but the results of these studies have been conflicting. Buller *et al.* (4) found a 67% 5-year survival in 11 women from ovarian cancer families, compared to 17% in 34 age-matched controls (4). The disease stage in the two groups was similar. However, a slightly larger study found the survival of 28 cases of familial ovarian cancer to be similar to that of 84 control cases matched for age and stage (5). There have also been three published studies that have investigated the influence of *BRCA1* mutations on survival in patients with ovarian cancer (6–8). Rubin *et al.* (6) found a median survival of 77 months in 43 *BRCA1* mutation carriers with advanced ovarian cancer, compared to 29 months for age- and stage-matched controls, a difference that was highly statistically significant. This study was subsequently criticized because of several possible biases. In particular, the possibility that a family history in mutation carriers may have led to surveillance bias has been suggested (9, 10), and likely differences in treatment between the two groups were highlighted (9, 11). A smaller study of 38 *BRCA1* carriers matched for stage, age, year of diagnosis, and histopathological features to 97 controls treated at same institution in Sweden found a similar survival in *BRCA1* carriers and controls for the first 4 years, after which survival was worse for the *BRCA1* group (7). This difference was not statistically significant. An uncontrolled Canadian study found the median survival in 44 *BRCA1*-associated cancers to be 31 months (8), which is similar to that reported by Johannsson *et al.* (11) for both mutation carriers and controls and to the controls in the study of Rubin *et al.* (6). No published studies have investigated survival in ovarian cancer patients with mutations in *BRCA2*.

Here, we carried out genetic analyses for mutations in *BRCA1* and *BRCA2* in families with site-specific ovarian cancer and breast-ovarian cancer families that are registered on the United Kingdom Coordinating Committee for Cancer Research (UKCCCR) Familial Ovarian Cancer Registry. We report our findings regarding the pathological features of ovarian cancer occurring in these families and of the clinical outcome for these patients according to whether an identifiable mutation in *BRCA1* or *BRCA2* was found in the family. We also compared the survival in familial ovarian cancer cases with or without a *BRCA1/2* mutation with a population-based control group matched on age and year of diagnosis.

MATERIALS AND METHODS

Patients. The UKCCCR Familial Ovarian Cancer Registry was used to identify cases of invasive epithelial ovarian cancer occurring in site-specific ovarian cancer families and breast-ovarian cancer families. Families with two or more confirmed cases of ovarian cancer are eligible for the register and are referred by oncologists, cancer geneticists, and general practitioners from

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Table 1 *Details of ovarian cancer families by number of affected members and results of BRCA1/2 mutation testing*

No. of ovarian cancer cases in family	No. of families			
	BRCA1	*BRCA2*	No mutation	Not tested
2	13	4	46	50
3	18	7	9	16
4	5		3	9
5+	10		4	3
Total	46	11	62	78
Total no. of cases	167	29	154	201

throughout the United Kingdom. Where possible, death certificates and/or medical notes were obtained to confirm reported cases of ovarian cancer. Histopathological details were obtained from hospital pathology reports. *BRCA1* and *BRCA2* mutation testing was carried out in families with at least two affected relatives with ovarian cancer and for which DNA samples from blood lymphocytes were available from at least one affected individual with ovarian cancer.

Sporadic cases of epithelial ovarian cancer were identified from the population-based East Anglian Cancer Registry, which has data on all cases registered in the East Anglian region since 1971. Case ascertainment is by multiple methods, and 91% of cases are confirmed by histopathology. Regular, active follow-up of all cases ensures that survival data are accurate. Two controls matched on age and year of diagnosis were identified for each familial case diagnosed after 1970 for whom complete follow-up data were available.

Mutation Detection. The entire coding sequence and splice junctions of *BRCA1* and *BRCA2* were screened for mutations using a combination of the protein truncation test and nonradioactive single-strand conformation analysis/heteroduplex analysis and sequence analysis (12, 13). All affected relatives with ovarian cancer from families in which a mutation was identified were assumed to carry that mutation.

Statistical Methods. We compared characteristics of tumors between groups by χ^2 tests. Kaplan-Meier survival probabilities were calculated, and differences were tested by the log-rank test.

The major difficulty in assessing survival in known mutation carriers in this study is that such cases are, by definition, selected by virtue of having survived long enough to be tested. Even if one includes all cases in the family, the fact that at least one case (the index case) must be sampled biases the series toward better survival. In addition, there is a potential bias introduced by increased surveillance of women with a family history. To minimize the effects of these biases, the principal survival comparison in this study was between ovarian cancer cases from mutation-positive families and cases from families who were tested but found to be negative. The latter group of familial cases will necessarily contain some *BRCA1* and *BRCA2* mutations that were not detected, together with "sporadic" cases and perhaps some due to other genes. To determine whether there was a survival difference between familial ovarian cancer in general and unselected cases, we performed a separate analysis in which all cases on the register (whether or not they could be tested) who have been diagnosed since 1971 were compared with population controls. Because this included the cases from families in which there was no living proband available for genetic testing, bias due to increased survival in the index case did not apply to this analysis.

RESULTS

Data from 197 families with 551 family members reported to be affected with epithelial ovarian cancer were available from the Familial Ovarian Cancer Register. The breakdown of these families according to the number of affected individuals in the family and the results of mutation testing are given in Table 1. An index case with ovarian cancer was screened for mutations in *BRCA1* and *BRCA2* in 119 families including 350 affected individuals. *BRCA1* mutations were identified in 46 families (39%) with 167 affected family members; *BRCA2* mutations were found in 11 families (9%) with 29 cases; and no mutation was identified in the remaining 62 families (52%) with 154 affected members.

Within-Family Case Comparisons. In the mutation-tested families, the diagnosis of invasive epithelial ovarian cancer was confirmed in 298 of 350 affected members. The clinical and pathological characteristics of these tumors are summarized in Table 2. Not all of the clinical data were available for all of the cases. The age at diagnosis in *BRCA1* associated tumors was slightly less than that for the other tumors, but we found no differences in histopathological type, grade, or stage according to mutation status. Complete survival data were available on 270 patients from mutation-tested families. The actuarial survival by mutation status is shown in Fig. 1, and a summary of the survival data is given in Table 3. There was no difference in survival between the three groups (log-rank test: $\chi^2 = 0.17$, 2 degrees of freedom, $P = 0.91$).

Comparison of Familial Cases and Population Controls. Two population control cases matched on age and year of diagnosis were identified for 274 confirmed cases of familial ovarian cancer diagnosed after 1970. The clinicopathological characteristics of these tumors are given in Table 2. Although the pathological types were similar, the relatively rare mucinous tumors occurred significantly less in the familial cases (2% compared to 12%; $P < 0.001$). There was also a significantly higher proportion of stage III and IV tumors in the familial cases (83%) than in the population controls (56%; $P = 0.001$). Data on tumor grade were not available for the population

Table 2 *Clinical and pathological characteristics of familial and sporadic epithelial ovarian cancer*

	All familial cases				All familial cases after 1970[a]	Population controls
	BRCA1	*BRCA2*	None	Not tested		
No. of cases	133	26	139	172	274	552
Mean age at diagnosis, yr	49.9	55.7	53.7	56.6	54.4	54.4
Histopathological type, *n* (%)						
Adenocarcinoma, unspecified	61 (59)	8 (36)	52 (44)	56 (54)	116 (51)	263 (48)
Mucinous adenocarcinoma	3 (3)	2 (9)	4 (3)	6 (6)	5 (2)	68 (12)
Serous adenocarcinoma	26 (25)	9 (41)	37 (32)	22 (21)	70 (31)	156 (28)
Endometrioid adenocarcinoma	9 (9)	2 (9)	15 (13)	8 (8)	22 (10)	34 (6)
Poorly differentiated adenocarcinoma	3 (3)	1 (5)	5 (4)	5 (5)	6 (3)	9 (2)
Other	2 (2)		4 (3)	6 (6)	8 (3)	22 (4)
Unknown/unspecified	29	4	22	69	47	
Degree of differentiation, *n* (%)						
Well	7 (10)	0	12 (17)	5 (8)		
Moderate	24 (35)	4 (33)	25 (35)	20 (33)		
Poor	37 (54)	8 (67)	35 (49)	36 (59)		
Unspecified	65	14	67	111		
Stage, *n* (%)						
I/II	2 (11)		7 (35)	3 (16)	7 (17)	108 (44)
III/IV	17 (89)	4 (100)	13 (65)	16 (84)	35 (83)	136 (56)
Unspecified	114	22	119	167	234	308

[a] Includes those with and without known mutation.

controls. The actuarial survival of these cases is shown in Fig. 2. Although the early survival in the two groups was similar, the population cases had a later survival advantage, which was statistically significant (log-rank test: $\chi^2 = 7.77$, 1 degree of freedom, $P = 0.005$).

DISCUSSION

We found no differences in the pathological subtypes of ovarian cancer between familial ovarian cancer that was associated with mutations in *BRCA1* or *BRCA2* and familial ovarian cancer that was not associated with any mutation, nor have we found any major difference between familial cases and population controls, although the relatively rare mucinous tumors were significantly less frequent among the familial cases. The finding that familial cases tended to present with a higher stage is based on relatively few data, particularly for the familial cases. Nevertheless, this observation may suggest that familial ovarian cancer is more aggressive than sporadic ovarian cancer.

We found no evidence for a difference in survival for women with ovarian cancer from families with mutations in *BRCA1* or *BRCA2* compared to women with ovarian cancer from families in which no mutation has been identified. There was also no difference in survival between cases due to the two genes, although the number of *BRCA2* cases was too small to make definitive statements about this group. However, misclassification of mutation status will bias the result toward the null. First, we have assumed that all patients with invasive ovarian cancer in families with identified mutations are carriers. This assumption will result in the misclassification of less than 10% of patients (14). A more serious misclassification is that current mutation detection techniques miss a significant proportion of mutations, so that all women from some families will have been erroneously classified as mutation negative. The sensitivity of mutation testing is not yet precisely known, but it is thought to be ~60–70% (15). The effect of this misclassification is that the true confidence limits on any observed survival difference would be wider than the observed limits. However, no survival difference was observed.

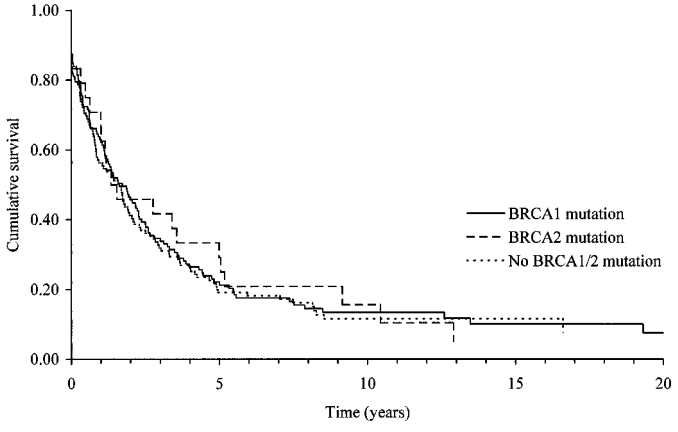

Fig. 1. Actuarial survival of hereditary invasive epithelial ovarian cancer by *BRCA1/2* mutation status.

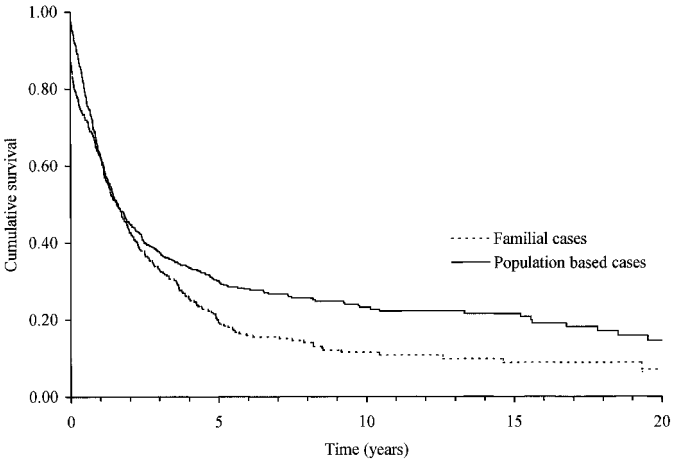

Fig. 2. Actuarial survival of hereditary ovarian cancer compared to population controls.

In contrast, the survival of familial cases as a whole was found to be significantly worse than for population controls. This finding may be a reflection of real biological differences between familial and sporadic epithelial ovarian cancer. Biological differences might be expected to be manifest not only by survival differences but also by differences in histopathological type and stage, differences that were, indeed, observed. Both histopathological type and stage are important predictors of prognosis, and inclusion of histopathological grade in a multivariate survival analysis reduced the survival difference between familial and sporadic cases to nonsignificance. Data on stage were sparse, but if the few familial tumors for which stage data were available were representative of all familial tumors, the difference in stage between familial and sporadic tumors could also account for some of the survival advantage of the sporadic cases.

An alternative explanation is that the observed survival difference is the result of bias. However, the expected biases that affect survival in familial cases—*i.e.*, selective ascertainment of ovarian cancer families with surviving cases and increased surveillance of women with a family history—would be expected to improve outcome for the familial cases. If these biases were operating, the true difference would be larger than that observed. Regional differences in survival may be more relevant because the population controls were selected from the East Anglian cancer registry, whereas the ovarian cancer families are from all over the United Kingdom. However, there are minimal regional differences in survival of ovarian cancer in the United Kingdom, and the 5-year survival for all ovarian cancer in East Anglia is similar to that for the rest of the country. Regional differences in all cause mortality may also account for some of the observed difference in survival because the standardized mortality ratio for East Anglia is lower than that for the United Kingdom as a whole. This is not likely to have a major impact because the mortality from the cancer itself is so much greater than that from other causes.

Our results are at odds with the findings from other studies, which

Table 3 *Summary of survival in women with invasive epithelial ovarian cancer*

	BRCA1	*BRCA2*	No mutation	All familial cases[a]	Population controls
No. of cases	127	24	119	274	552
No. of deaths	112	22	104	242	396
Median survival, months	20.6	16.0	19.5	19.5	18.6
2-year survival, % (95% CI[b])	46 (38–54)	46 (26–66)	40 (31–49)	43 (37–49)	45 (40–50)
5-year survival, % (95% CI)	21 (14–28)	25 (8–42)	19 (12–26)	20 (15–25)	30 (26–34)

[a] Diagnosed after 1970, including those with and without known mutation.
[b] CI, confidence interval.

have suggested similar (5, 7) or improved (4, 6) survival in familial or *BRCA1*-associated ovarian cancer. However, in three of these studies, the familial/mutation cases were matched with sporadic controls for several factors, including stage at diagnosis. Stage is likely to reflect not only the mode of diagnosis but also the biological characteristics of the tumor. More aggressive tumors are likely to present at a later stage, so matching for this characteristic may have the effect of reducing or removing a true survival difference between the groups. Indeed, when we restricted our survival analysis to the stage III/IV cancers, we found no difference between the familial and population cases, although the number of familial cases was small.

We conclude that survival in hereditary ovarian cancer is, if anything, worse than in sporadic disease, perhaps reflecting a real difference in biology that is analogous to that observed in breast cancer.

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