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Report of Endometrial Cancer in Australian *BRCA1* and *BRCA2* Mutation-Positive Families

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There is evidence that tamoxifen treatment of *BRCA1* and *BRCA2* carriers for prior breast cancer increases risk of endometrioid subtype endometrial cancer (EC), and suggestive evidence that *BRCA1* and *BRCA2* mutation carriers may be predisposed to EC in the absence of tamoxifen exposure. We assessed the association of EC with *BRCA1* or *BRCA2* mutation status in Australasian breast-ovarian families. Report of at least one case of EC was significantly greater in *BRCA1*-positive families (35/218 (16%); p = .03) and non-significantly greater in *BRCA2*-positive families (23/189 (12%); p = .6), compared to high-risk breast cancer families without a *BRCA1*/2 mutation (86/796 (11%)). EC was the first/concurrent cancer for 41% of EC cases with multiple cancer diagnoses from *BRCA1/2* families, and early onset for most of these diagnoses. Mutation status was imputed for ungenotyped individuals from 57 *BRCA1/2* pedigrees reporting EC using BRCAPRO. Effects of genotype on EC diagnosis age, and interaction with tamoxifen therapy, were assessed using Cox proportional hazards regression analysis. EC risk was non-significantly marginally greater for *BRCA1* carriers (hazard ratio = 1.25, 95%CI = 0.65–2.41), and *BRCA2* carriers (HR = 1.12, 95%CI = 0.51–2.45), compared to non-carrier family members. Tamoxifen therapy was highly significantly associated with EC (HR = 6.68, 95%CI = 3.12–15.15; $p = 1.7 \times 10^{-6}$) in *BRCA1/2* families, with no evidence for interaction between tamoxifen therapy and *BRCA1/2* genotype. Our family-based study supports a 7-fold increase in EC risk with tamoxifen exposure for female family members from *BRCA1*/2 families. Early onset EC in carriers without tamoxifen use suggests that further study is required to assess association of modest EC risk with *BRCA1*/2 mutation status alone.

■ **Keywords:** BRCA1, BRCA2, endometrial cancer, tamoxifen

There is evidence in the literature that germline mutations in the breast cancer predisposition genes *BRCA1* and *BRCA2* mutations may predispose female carriers to risk of endometrial cancer (EC), in particular, the aggressive serous subtype. Several case reports and small studies described founder Ashkenazi *BRCA1* or *BRCA2* mutations in primary EC patients (Biron-Shental et al., 2006; Ciernikova et al., 2006; Hornreich et al., 1999; Lavie et al., 2005; Lavie et al., 2000; Lavie et al., 2004), with some suggestion that mutation-positive EC patients were more likely to occur in breast-ovarian cancer families and that risk may be increased for the aggressive serous subtype of EC in particular. A subset of these studies reported prior breast cancer diagnosis for 10% of the EC patients (Biron-Shental et al., 2006; Lavie et al., 2004). In addition, a non-significant 2.7-fold increased risk of EC has been reported in relatives of Ashkenazi ovarian cancer *BRCA1/2* carriers, and a 6.5-fold increased incidence to age 75 was estimated for first-degree relatives of carriers of the Ashkenazi founder mutations versus partially screened non-carriers (Moslehi et al., 2000). However, three other studies have reported no association between *BRCA1/2* mutations and EC (Barak et al., 2010; Goshen et al., 2000; Levine et al., 2001). The first study used poor sensitivity

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mutation screening, 1-2 exons plus three Jewish founder mutations, in a non-Jewish EC cohort (Goshen et al., 2000). The second and third studies screened Jewish predominantly endometrioid EC patients for common Jewish mutations and identified *BRCA1* and *BRCA2* mutations at frequencies similar to the baseline frequency of ~2% in the general population (Barak et al., 2010; Levine et al., 2001). In addition, a large prospective study reported an increased EC risk in a cohort of 857 *BRCA1/2* carriers (SIR = 5.3; Beiner et al., 2007). Analysis of the six EC patients identified provided evidence that tamoxifen treatment for prior breast cancer was a major contributor to endometrioid EC risk in *BRCA1/2* carriers (Beiner et al., 2007), and there was also suggestive evidence for an increased risk of EC (SIR = 2.7) in women not exposed to tamoxifen.

Studies assessing cancer incidence in *BRCA1* and *BRCA2* carriers from large breast cancer families ascertained through cancer clinics have reported a modest increased in risk of endometrial/uterine cancer of unspecified subtype, and provide additional support for a modest increased risk of EC for *BRCA1* carriers particularly. Analysis of 11,847 individuals from 699 *BRCA1* families revealed a significantly increased relative risk (RR) of 2.65 (1.69–4.16; $P < .001$) for the development of EC (Thompson & Easton, 2002). Analysis of two large *BRCA2* families reported a non-significant RR of 2.37 (Easton et al., 1997), and analysis of 3728 individuals from 173 *BRCA2* families showed a non-significant RR of 1.25 (Breast Cancer Linkage Consortium, 1999). These reports did not assess the relevance of tamoxifen exposure in relation to EC risk among *BRCA1* or *BRCA2* mutation carriers.

We undertook a study to assess whether there is an increased incidence of EC in an Australasian cohort of *BRCA1* and *BRCA2* mutation-positive families. We also explored whether this risk is specifically associated with tamoxifen use, and assessed histological subtype of EC cases where information was available.

Methods

Patient Cohort

High-risk breast cancer families were ascertained through the Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab; Mann et al., 2006), and included families with or without reported *BRCA1/2* mutations. Deleterious mutations included truncating and splice site mutations, large deletions, variants classified clinically important on BIC (http://research.nhgri.nih.gov/bic), and missense substitutions classified as pathogenic, using multifactorial likelihood approaches (Chenevix-Trench et al., 2006). Mutation results for probands (generally the youngest affected family member) were from diagnostic testing at entry into kConFab, and/or research testing after recruitment into kConFab. Mutation testing included full sequencing, or denaturing high performance liquid chromatography (DHPLC) and sequencing, and multiplex ligation-dependent probe amplification (MLPA) testing for large deletions. Relatives of proband carriers were screened for the family mutation only.

Each participating family member completed a detailed questionnaire, including questions relating to cancer diagnoses, prophylactic surgery, tamoxifen therapy use, and clinical trial participation. Information on tamoxifen use was limited to past or present use, with no dose or duration of treatment information available. Each participant in an individual family provided a detailed family history of cancer, including reports of cancer for non-participating relatives, with the final family pedigree including all information on reported cancers assimilated across the family. As part of core kConFab activities, reported cancers of participants were verified wherever possible from clinical records (pathology reports, doctor's notes), and matching to state cancer registries. Pathology reports were collected for data abstraction (undertaken by ABS and CS), and where possible archival tumor specimens of endometrial/uterine tumors in individuals with positive or unknown *BRCA1/2* mutation status were obtained for pathology review (undertaken by CS). A large number of EC diagnoses were before 1980 (65% for *BRCA1*, 45% for *BRCA2*), restricting access to clinical records and tumor blocks for verification and review. In addition, while age at EC onset ranged widely (47–70y for *BRCA1*, 33–86y for *BRCA2*), these individuals were generally from an early birth cohort (33 and 14 with year of birth ≤ 1930 for *BRCA1* and *BRCA2* families, respectively), limiting biospecimen availability for genotyping of individuals with reported EC.

Ethical approvals were obtained from the Human Research Ethics Committees of the Queensland Institute of Medical Research, the Peter MacCallum Cancer Centre, and all participating hospitals and cancer registries. Written informed consent was obtained from each participant.

Statistical Analysis

The frequency of reported EC in families with a known *BRCA1* or *BRCA2* mutation was compared to that in 'high risk breast cancer families' without a known mutation using a chi-squared test. Families were included as positive for a report of EC if report of endometrial or uterine cancer was recorded for at least one individual. These descriptive analyses included 796 non-*BRCA1/2* families, 218 *BRCA1* families, and 189 *BRCA2* families.

Fifty-seven pedigrees from *BRCA1/2*-positive families reporting endometrial cancer were included in endometrial cancer risk analyses. We used the R BayesMendel package (Version 2.0–1) to implement the BRCAPRO model and incorporate *BRCA1/BRCA2* genotyping information, to estimate mutation carrier probabilities for all untested individuals in known mutation-positive families (Parmigiani et al., 2008). It was necessary to break marital loops in two pedigrees for the BayesMendel peeling algo-

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rithm. Resulting carrier probabilities were used as predictors in a Cox proportional hazards model. For imputation of mutation status, breast or ovarian cancer-affected females were censored at age of first cancer diagnosis, and unaffected individuals were censored at the earliest of age at interview, death, prophylactic mastectomy or prophylactic oophorectomy. The final dataset included mutation status information for 1090 female individuals (482 measured, 608 imputed). Cox proportional hazards regression analysis of the effects of genotype on age at diagnosis of EC, and interaction with tamoxifen therapy, was carried out using the *survival* package (Therneau & Lumley, 2008) in the R statistical programming environment (R Core Development Team, 2008). For Cox regression, all individuals reporting EC were censored at age at diagnosis of EC (irrespective of prior cancer report), all individuals with no EC but reporting hysterectomy were censored at age of surgical procedure (irrespective of breast or ovarian cancer diagnosis), and individuals without hysterectomy and no report of EC were censored at age of interview. Individuals without information on tamoxifen use were considered to have no exposure to tamoxifen if censoring occurred before 1995. Statistical tests were 2-sided.

Results

Frequency of Endometrial Cancer Report in Breast and Breast-Ovarian Cancer Families

At the time of analysis, the kConFab resource had information on mutation status for 1,203 families (Table 1): 218 families with a *BRCA1* mutation in at least one individual; 189 with a *BRCA2* mutation; and 796 with no known *BRCA1* or *BRCA2* mutation. EC was reported in 48 women from 34 *BRCA1* families, 22 women from 22 *BRCA2* families, and a single individual from a family with a mutation in both *BRCA1* and *BRCA2*. There were 8 *BRCA1* families reporting two ECs, two families with three cases each, and a single family with four cases. The EC was verified for 17/49 cancers for *BRCA1* families, and 10/23 cancers for *BRCA2* families.

EC was reported significantly less often by non-*BRCA1/2* families (11%) than by *BRCA1* mutation-positive families (16%; $p = .03$), but not compared to *BRCA2* mutation-positive families (12%; $p = .6$). Most non-*BRCA1/2* families reporting EC (72/86, 83%) had undergone a high level of *BRCA1/2* gene mutation testing in the youngest living affected family member (DHPLC or full sequencing, and MLPA testing). The generic description of families was compared for those reporting EC to those with no report of EC. *BRCA1* families with EC presented somewhat more commonly with ovarian cancer (with or without male breast cancer), but these differences were not significant ($p = .2$). Although *BRCA2* families with EC were more common in families with female breast, male breast and ovarian cancer (21.7% vs 4.2%; $p = .005$), there was no overall increased presentation with ovarian cancer in family members when the comparison also included families with female breast and ovarian cancer ($p = .8$).

Mutation Status and Other Cancer Diagnoses of Endometrial Cancer Cases From BRCA1 and BRCA2 Families

Genotyping information was generated for 21 EC cases with DNA available. The mutation status for EC cases was

TABLE 1

Characteristics of kConFab Families Reporting Endometrial Cancer[a]

Endometrial cancer case(s) reported	*BRCA1*	(%)	*BRCA2*	(%)	non-*BRCA1/2*	(%)
No	183	(83.9)	166	(87.8)	710	(89.2)
Yes	35	(16.1)	23	(12.2)	86	(10.8)
Total	*218*		*189*		*796*	
P value for frequency comparison to non-*BRCA1/2*		*0.03*		*0.6*		
Description of families reporting endometrial cancer[b]						
Female breast	9	(25.7)	11	(47.8)	59	(68.6)
Female breast and ovary	24	(68.6)	5	(21.7)	21	(24.4)
Female breast, male breast and ovary	2	(5.7)	5	(21.7)	1	(1.2)
Female breast, male breast	0	(0.0)	2	(8.7)	5	(5.8)
Male breast	0	(0.0)	0	(0.0)	0	(0.0)
Other	0	(0.0)	0	(0.0)	0	(0.0)
Description of families with no reported endometrial cancer[b]						
Female breast	61	(33.3)	77	(46.4)	493	(69.4)
Female breast and ovary	114	(62.3)	61	(36.7)	166	(23.4)
Female breast, male breast and ovary	3	(1.6)	7	(4.2)	9	(1.3)
Female breast, male breast	3	(1.6)	19	(11.4)	34	(4.8)
Male breast	0	(0.0)	2	(1.2)	3	(0.4)
Other	2	(1.1)	0	(0.0)	5	(0.7)

Note: [a] A single family carried both a pathogenic *BRCA1* and a pathogenic *BRCA2* mutation.
[b] Based on reports of female breast cancer, male breast cancer, and ovarian cancer only.

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TABLE 2

Characteristics of Mutation Carriers and Possible Mutation Carriers with Reported Endometrial Cancer from BRCA1/2 families

	BRCA1 carrier	*BRCA1* unknown	*BRCA2* carrier	*BRCA2* unknown	Total
Reported cancer(s) in addition to endometrial cancer[a]					
Breast	2	4	5	2	13
Ovarian	0	2	0	0	2
Ovarian and breast	1	0	1	0	2
None	1	31	0	11	43
Proportion carriers or possible carriers with additional cancers	3/4	6/37	6/6	2/13	17/60
Reported cancer(s) synchronous with or *after* endometrial cancer diagnosis[b]					
Breast	1	2	3	0	6
Ovarian	0	1	0	0	1
Ovarian and breast	0	0	0	0	0
Proportion carriers or possible carriers with cancers after or synchronous with endometrial cancer	1/4	3/37	3/6	0/13	7/60

Note: [a] Based on reports of breast and ovarian cancer only. Includes reported diagnoses before, after or synchronous to reported endometrial cancer diagnosis.
[b] Ages at diagnosis of endometrial cancers were: 66y (*BRCA1* carrier); 32y, 43y, and 48y (*BRCA1* unknown); and 33y, 39y, and 52y (*BRCA2* carriers).

positive for 4/12 genotyped individuals from *BRCA1* families, and 6/9 genotyped individuals from *BRCA2* families. A number of the individuals with reported EC and positive or unknown mutation status *also* reported another cancer (17/60 (28%) individuals, detailed in Table 2). This included 3/4 known *BRCA1* carriers, and 6/6 known *BRCA2* mutation carriers, totaling 9/10 known mutation carriers. Approximately 15% of possible mutation carriers (6/37 *BRCA1* and 2/13 *BRCA2*) also reported cancers that are known to be associated with *BRCA1* and *BRCA2* positive mutation status. The timing of these cancers in relation to endometrial cancer diagnosis was assessed. EC diagnosis was the first or concurrent primary cancer for 7/17 (41%) reports of multiple cancer diagnoses in known or possible mutation carriers. This included 4/4 confirmed mutation carriers (1 *BRCA1*, and 3 *BRCA2*).

The age at EC diagnosis for individuals with known positive or unknown *BRCA1* mutation status (i.e., excluding known mutation-negative endometrial cases) ranged from 25y to 91y (average 54y). A considerable number of these cases (17/41, 42%) were diagnosed ≤ 50y, and only 3 of these early onset cases reported a prior breast cancer. EC cases with known positive or unknown *BRCA2* mutation status ranged in age at onset from 33y to 84y (average 57y), with 30% (6/19) diagnosed under 50y, and only 2 of these reporting a prior breast cancer. Within the small subset of endometrial cases with synchronous or subsequent breast or ovarian cancer(s), the majority (5/7, 71%) had very early onset disease, with 3 diagnosed under 40y, and another 2 at 43y and 48y.

Tamoxifen Use and Histological Subtype of Endometrial Cancer Cases From BRCA1 and BRCA2 Families.

The relationship between tamoxifen treatment and breast and/or EC diagnosis was also assessed for all women in *BRCA1* and *BRCA2* families. Data were recorded for 445 women, with only 12 reporting tamoxifen use prior to censor age. Of these, 7 were mutation carriers (4 *BRCA1*, 3 *BRCA2*) and 5 of these individuals developed EC after breast cancer (2 *BRCA1*, 3 *BRCA2*). Age at first tamoxifen use was post-menopausal for all but one woman (a *BRCA2* carrier). Another 4 patients reporting tamoxifen use were mutation-negative, two of whom developed EC after breast cancer. The remaining individual of unknown mutation status developed breast and ovarian cancer but not EC. EC was reported in 3.0% of women with no known tamoxifen use (13/433), and in 2.4% of women in whom tamoxifen data were not available (51/2092). Most of the latter (>80%) were unlikely to have been exposed to tamoxifen, since their age at censorship was prior to 1995 when tamoxifen was made available to individuals unaffected by breast cancer in Australia through the IBIS-1 trial. Only a single mutation carrier reported use of hormone replacement therapy prior to EC diagnosis.

Information on histological subtype was available for the subset of verified ECs only: 6 known mutation carriers (5 endometrioid carcinomas and 1 endometrial stromal sarcoma), and 1 with unknown mutation status (carcinosarcoma). The stromal sarcoma and carcinosarcoma were diagnosed in individuals with a prior breast cancer from *BRCA2* families, and both had received tamoxifen therapy. Of the 5 endometrioid cancers (2 *BRCA1*, 3 *BRCA2*), two occurred in women with no prior breast cancers or tamoxifen use, and the remaining three were diagnosed in women with prior breast cancer and tamoxifen treatment. That is, there were no serous papillary tumors reported in this series, and tamoxifen use was reported by both the women with the rare aggressive sarcoma/carcinosarcoma subtype.

Association Between BRCA1 and BRCA2 Mutation Status and Endometrial Cancer Risk

The Cox regression analysis was carried out on the 57 pedigrees where a *BRCA1/2* mutation had been identified, and one or more cases of EC were present. Within these

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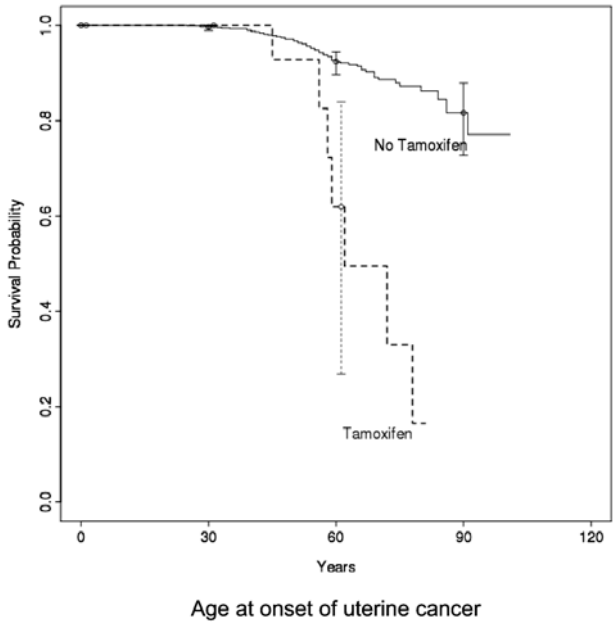

FIGURE 1

Disease-free survival curves for endometrial cancer versus tamoxifen therapy in families segregating *BRCA1* or *BRCA2* mutations.

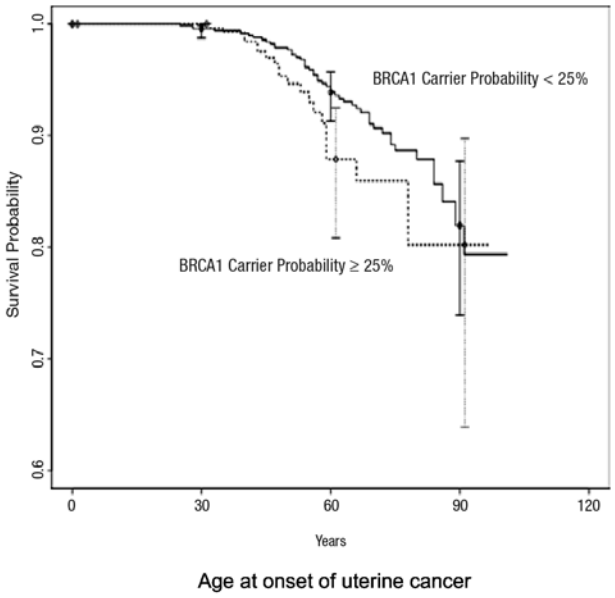

FIGURE 2

Disease-free survival curves for endometrial cancer versus *BRCA1* genotype.

families, diagnosis of EC was not significantly associated with *BRCA1* mutation status (Hazard Ratio = 1.25, 95%CI = 0.65–2.41), or *BRCA2* mutation status (HR = 1.12, 95%CI = 0.51–2.45), although risk estimates were marginally greater than unity in both instances. Tamoxifen therapy was highly significantly associated with EC (HR = 6.88, 95%CI = 3.12–15.15; $p = 1.7 \times 10^{-6}$; See Figure 1). Adjustment for tamoxifen use yielded risk estimates of 1.14 (0.58–2.25) for *BRCA1* carriers and 0.84 (0.37–1.91) for *BRCA2* carriers. Tests for interaction between tamoxifen therapy and *BRCA1* or *BRCA2* genotype were not significant ($p = .2$). Nevertheless, examination of the survival plot for *BRCA1* carriers in particular suggested that a very modest association with mutation status alone cannot be excluded (Figure 2).

Discussion and Conclusions

Some studies of Ashkenazi founder mutation carriers have suggested an increased risk of EC (Biron-Shental et al., 2006; Hornreich et al., 1999; Lavie et al., 2005; Lavie et al., 2004; Moslehi et al., 2000), in particular, the serous subtype, and increased risk of EC in *BRCA1* and *BRCA2* carriers is supported by analysis of cancer incidence in mutation carriers from large breast cancer families showing a modest 2-fold increased EC risk in *BRCA1* carriers especially (Breast Cancer Linkage Consortium, 1999; Easton et al., 1997; Thompson & Easton, 2002). However, it is possible that the increased risk of EC in these cohorts enriched for breast cancer may be due in part to tamoxifen exposure. Tamoxifen is a selective estrogen-receptor modulator that has been used in treatment of pre- and post-menopausal ER-positive breast cancer for over 20 years (Early Breast Cancer Trialists, 1998; Osborne, 1998). There is a clear association of tamoxifen use with increased EC risk, with reported relative risks including 2.4-fold from prevention studies ($p = 0.0005$), 3.4-fold from adjuvant studies ($p = .0002$; Cuzick et al., 2003), and 2.2-fold from a very large retrospective study of 39,451 US breast cancer patients initially treated with tamoxifen (Curtis et al., 2004). Risk appears to be mainly seen in women aged 50 years or more, and most studies with relevant data on tumor histology do suggest an increase in the proportion of poor prognosis non-endometrioid EC subtypes such clear cell, serous papillary, malignant mixed mullerian tumors, as well as stromal sarcoma uterine cancers (Arenas et al., 2006; Bergman et al., 2000; Fisher et al., 1994; Kloos et al., 2002; Magriples et al., 1993; Mignotte et al., 1998; Moinfar et al., 2007; Saadat et al., 2007).

Although interventional studies have been carried out among individuals at high risk of breast cancer (Cuzick et al., 2003), to date no tamoxifen studies were specifically designed to report on the subsequent rate of EC development in *BRCA1* and *BRCA2* mutation carriers. However, one prospective study of *BRCA1* and *BRCA2* carriers has shown that tamoxifen treatment for prior breast cancer was a major contributor to the development of endometrioid endometrial carcinoma, with an 11-fold risk in the subset of women exposed to tamoxifen (Beiner et al., 2007). Using a family-based design, our results support an increase in risk among *BRCA1/2* carriers with tamoxifen exposure — with an observed 7-fold increase in EC risk for family members on tamoxifen regardless of their mutation status. The confidence intervals are sufficiently

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broad (3.1–15.2) that they overlap with the previously reported 11-fold risk among *BRCA1/2* carriers (Beiner et al., 2007), and also with risks of 2.4 (1.5–4.0) to 3.4 (1.8–6.4) reported for patients in the general population (Cuzick et al., 2003). There was no evidence for an interaction between tamoxifen use and mutation status. There was also no statistically significant evidence for an increased risk of EC with *BRCA1* or *BRCA2* mutation status alone. However, only a modest ~2.5-fold risk is indicated from previous studies of large *BRCA1* and *BRCA2* families (Breast Cancer Linkage Consortium, 1999; Easton et al., 1997; Thompson & Easton, 2002), the upper confidence limits of risk estimates were 2.4 for *BRCA1* carriers and 2.5 for *BRCA2* carriers. This suggests that any risk associated with mutation status in the absence of tamoxifen use would be modest, and that analysis of a much larger sample of *BRCA1* and *BRCA2* families is required to assess this possibility.

It is also interesting to note that EC was the first or concurrent malignancy in a substantial proportion of known *BRCA1/2* carriers reporting multiple cancer diagnoses, and that these included very early onset cancers (diagnosed <40) with no prior breast cancers or tamoxifen use. It is important to recall that although it is now well recognized that germline mutations in either *BRCA1* or *BRCA2* are associated with an increased risk of primary peritoneal and fallopian tube cancers, initial analyses of *BRCA1* and *BRCA2* mutation carriers ascertained largely through clinic ascertainment of breast-ovarian families showed an increased risk of primary peritoneal cancers in *BRCA1* carriers, but did not show increased risk for fallopian tube carcinomas in *BRCA1* or *BRCA2* carriers (Breast Cancer Linkage Consortium, 1999; Easton et al., 1997; Thompson & Easton, 2002). Thus, at the present time, it would be prudent to allow continued debate about a possible role of *BRCA1/2* in endometrial cancer predisposition.

In relation to the previously reported association of *BRCA1/2* mutation status with serous EC, our data provide no evidence for this. The majority of cases with known histology were endometrioid carcinomas, and previous tamoxifen use is most likely to account for the endometrial stromal sarcoma identified in a *BRCA2* carrier, and the endometrial carcinosarcoma developing in a woman of unknown mutation status (Arenas et al., 2006; Kloos et al., 2002; Moinfar et al., 2007). It is unlikely that our results were confounded by the fact that uterine papillary serous cancer as a histologic entity was described in 1982, since confirmation by pathology report (and thus verification of histological classification) was not possible for any cases with known positive mutation status diagnosed before this date. An appropriately designed and well-powered study would be required to address the hypothesis that these rare tumors are more common in *BRCA2 (or BRCA1)* mutation carriers, and the role of tamoxifen use in their development.

There was no convincing evidence from our analysis that EC was more likely to be reported in *BRCA1/2* families that also report ovarian cancer, as has been suggested previously in the literature. We also recognise that it is possible that some ovarian cancers in our study may have been misreported by participants as ECs, or were ovarian primaries with endometrial involvement, given the limited information on cancer verification. It is extremely unlikely, however, that the association between tamoxifen use and EC report is due to misreporting, since there is no known association between tamoxifen use and increased ovarian cancer risk (Vicus et al., 2009).

Our findings are likely to impact the clinical management of women from hereditary breast ovarian families, with an identified mutation in *BRCA1*/*BRCA2*. Chemoprevention is available to such women at increased risk for breast cancer, and results of this study support the argument that if tamoxifen is to be used, it is done so with caution and only after careful counseling. In women contemplating bilateral salpingo-oophorectomy (BSO), the additional removal of the uterus may, facilitate the use of tamoxifen as a chemopreventative agent for breast cancer risk reduction. This might be particularly relevant for women undergoing a late BSO when the potential for a reduction in breast cancer risk (associated with oophorectomy) is less likely. Raloxifene use may be more appropriate for women with a retained uterus, with results from the STAR P-2 trial indicating that long-term raloxifene use attains similar effectiveness to tamoxifen in preventing invasive breast cancer but with significantly lower risk of EC (Vogel et al., 2006; Vogel et al., 2010). At present our findings do not have implications for the criteria used for selection of families for *BRCA1/2* mutation screening, but further studies may highlight the importance of early onset primary EC cases in recognition of breast-ovarian families potentially suitable for mutation screening.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

DD participated in study design, performed most statistical analyses, and drafted aspects of the manuscript.YA participated in study design, and assisted with manuscript drafting.CS critically reviewed tumor pathology data and slides, and assisted with manuscript drafting. JY participated in design and execution of the study, and assisted with manuscript drafting. ABS conceived the study, was responsible for data collation and manipulation for statistical analysis, performed some statistical analyses, and drafted the manuscript. All authors critically reviewed the manuscript, and approved the final draft.

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References

Arenas, M., Rovirosa, A., Hernandez, V., Ordi, J., Jorcano, S., Mellado, B., & Biete, A. (2006). Uterine sarcomas in breast cancer patients treated with tamoxifen. *International Journal of Gynecological Cancer, 16*, 861–865.

Barak, F., Milgrom, R., Laitman, Y., Gemer, O., Rabinovich, A., Piura, B., Anteby, E., Baruch, G. B., Korach, J., & Friedman, E. (2010). The rate of the predominant Jewish mutations in the BRCA1, BRCA2, MSH2 and MSH6 genes in unselected Jewish endometrial cancer patients. *Gynecologic Oncology, 119*, 511–515.

Beiner, M. E., Finch, A., Rosen, B., Lubinski, J., Moller, P., Ghadirian, P., Lynch, H. T., Friedman, E., Sun, P., & Narod, S. A. (2007). The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. *Gynecologic Oncology, 104*, 7–10.

Bergman, L., Beelen, M. L., Gallee, M. P., Hollema, H., Benraadt, J., & van Leeuwen, F. E. (2000). Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet, 356*, 881–887.

Biron-Shental, T., Drucker, L., Altaras, M., Bernheim, J., & Fishman, A. (2006). High incidence of BRCA1-2 germline mutations, previous breast cancer and familial cancer history in Jewish patients with uterine serous papillary carcinoma. *European Journal of Surgical Oncology*, *32*, 1097–1100.

Breast Cancer Linkage Consortium. (1999). Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. *Journal of the National Cancer Institute, 91*, 1310–1316.

Chenevix-Trench, G., Healey, S., Lakhani, S., Waring, P., Cummings, M., Brinkworth, R., Deffenbaugh, A. M., Burbidge, L. A., Pruss, D., Judkins, T., Scholl, T., Bekessy, A., Marsh, A., Lovelock, P., Wong, M., Tesoriero, A., Renard, H., Southey, M., Hopper, J. L., Yannoukakos, K., Brown, M., Easton, D., Tavtigian, S. V., Goldgar, D., & Spurdle, A. B. (2006). Genetic and histopathologic evaluation of BRCA1 and BRCA2 DNA sequence variants of unknown clinical significance. *Cancer Research, 66*, 2019–2027.

Ciernikova, S., Tomka, M., Kovac, M., Stevurkova, V., & Zajac, V. (2006). Ashkenazi founder BRCA1/BRCA2 mutations in Slovak hereditary breast and/or ovarian cancer families. *Neoplasma, 53*, 97–102.

Curtis, R. E., Freedman, D. M., Sherman, M. E., & Fraumeni, J. F., Jr. (2004). Risk of malignant mixed mullerian tumors after tamoxifen therapy for breast cancer. *Journal of the National Cancer Institute, 96*, 70–74.

Cuzick, J., Powles, T., Veronesi, U., Forbes, J., Edwards, R., Ashley, S., & Boyle, P. (2003). Overview of the main outcomes in breast-cancer prevention trials. *Lancet, 361*, 296–300.

Early Breast Cancer Trialists', Collaborative Group (1998). Tamoxifen for early breast cancer: An overview of the randomised trials. *Lancet, 351*, 1451–1467.

Easton, D. F., Steele, L., Fields, P., Ormiston, W., Averill, D., Daly, P. A., McManus, R., Neuhausen, S. L., Ford, D., Wooster, R., Cannon-Albright, L. A., Stratton, M. R., & Goldgar, D. E. (1997). Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12–13. *American Journal of Human Genetics, 61*, 120–128.

Fisher, B., Costantino, J. P., Redmond, C. K., Fisher, E. R., Wickerham, D. L., & Cronin, W. M. (1994). Endometrial cancer in tamoxifen-treated breast cancer patients: Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 [see comments]. *Journal of the National Cancer Institute, 86*, 527–537.

Goshen, R., Chu, W., Elit, L., Pal, T., Hakimi, J., Ackerman, I., Fyles, A., Mitchell, M., & Narod, S. A. (2000). Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? *Gynecologic Oncology, 79*, 477–481.

Hornreich, G., Beller, U., Lavie, O., Renbaum, P., Cohen, Y., & Levy-Lahad, E. (1999). Is uterine serous papillary carcinoma a BRCA1-related disease? Case report and review of the literature. *Gynecologic Oncology, 75*, 300–304.

Kloos, I., Delaloge, S., Pautier, P., Di Palma, M., Goupil, A., Duvillard, P., Cailleux, P. E., & Lhomme, C. (2002). Tamoxifen-related uterine carcinosarcomas occur under/after prolonged treatment: Report of five cases and review of the literature. *International Journal of Gynecology and Cancer, 12*, 496–500.

Lavie, O., Ben-Arie, A., Pilip, A., Rennert, G., Cohen, Y., Feiner, B., & Auslnader, R. (2005). BRCA2 germline mutation in a woman with uterine serous papillary carcinoma — Case report. *Gynecologic Oncology, 99*, 486–488.

Lavie, O., Hornreich, G., Ben Arie, A., Renbaum, P., Levy-Lahad, E., & Beller, U. (2000). BRCA1 germline mutations in women with uterine serous papillary carcinoma. *Obstetrics and Gynecology, 96*, 28–32.

https://doi.org/10.1375/twin.14.2.111 Published online by Cambridge University Press

Lavie, O., Hornreich, G., Ben Arie, A., Rennert, G., Cohen, Y., Keidar, R., Sagi, S., Levy-Lahad, E., Auslander, R., & Beller, U. (2004). BRCA germline mutations in Jewish women with uterine serous papillary carcinoma. *Gynecologic Oncology, 92*, 521–524.

Levine, D. A., Lin, O., Barakat, R. R., Robson, M. E., McDermott, D., Cohen, L., Satagopan, J., Offit, K., & Boyd, J. (2001). Risk of endometrial carcinoma associated with BRCA mutation. *Gynecologic Oncology, 80*, 395–398.

Magriples, U., Naftolin, F., Schwartz, P. E., & Carcangiu, M. L. (1993). High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *Journal of Clinical Oncology, 11*, 485–490.

Mann, G. J., Thorne, H., Balleine, R. L., Butow, P. N., Clarke, C. L., Edkins, E., Evans, G. M., Fereday, S., Haan, E., Gattas, M., Giles, G. G., Goldblatt, J., Hopper, J. L., Kirk, J., Leary, J. A., Lindeman, G., Niedermayr, E., Phillips, K. A., Picken, S., Pupo, G. M., Saunders, C., Scott, C. L., Spurdle, A. B., Suthers, G., Tucker, K., & Chenevix-Trench, G. (2006). Analysis of cancer risk and BRCA1 and BRCA2 mutation prevalence in the kConFab familial breast cancer resource. *Breast Cancer Research, 8*, R12.

Mignotte, H., Lasset, C., Bonadona, V., Lesur, A., Luporsi, E., Rodier, J. F., Cutuli, B., Lasry, S., Mauriac, L., Granon, C., Kerr, C., Giard, S., Hill, C., de Lafontan, B., de Gislain, C., D'Anjou, J., Fondrinier, E., Lefeuvre, C., Parache, R. M., & Chauvin, F. (1998). Iatrogenic risks of endometrial carcinoma after treatment for breast cancer in a large French case-control study. Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC). *International Journal of Cancer, 76*, 325–330.

Moinfar, F., Azodi, M., & Tavassoli, F. A. (2007). Uterine sarcomas. *Pathology, 39*, 55–71.

Moslehi, R., Chu, W., Karlan, B., Fishman, D., Risch, H., Fields, A., Smotkin, D., Ben-David, Y., Rosenblatt, J., Russo, D., Schwartz, P., Tung, N., Warner, E., Rosen, B., Friedman, J., Brunet, J. S., & Narod, S. A. (2000). BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. *American Journal of Human Genetics, 66*, 1259–1272.

Osborne, C. K. (1998). Steroid hormone receptors in breast cancer management. *Breast Cancer Research and Treatment, 51*, 227–238.

Parmigiani, G., Chen, S., Wang, W., Katki, H., Blackford, A., Aguilar, O., Chen, S., Gudbjartsson, D.F., Zhou, K., & Iverson, E.S. (2008). BayesMendel: Determining carrier probabilities for cancer susceptibility genes. (Version 2.0–1).

R Core Development Team. (2008). *R: A language and environment for statistical computing*. Retrieved from http://www.R-project.org

Saadat, M., Truong, P. T., Kader, H. A., Speers, C. H., Berthelet, E., McMurtrie, E., & Olivotto, I. A. (2007). Outcomes in patients with primary breast cancer and a subsequent diagnosis of endometrial cancer : comparison of cohorts treated with and without tamoxifen. *Cancer, 110*, 31–37.

Therneau, T., & Lumley, T. (2008). Survival: Survival analysis, including penalised likelihood. R package version 2.34–1.

Thompson, D., & Easton, D. F. (2002). Cancer incidence in BRCA1 mutation carriers. *Journal of the National Cancer Institute, 94*, 1358–1365.

Vicus, D., Rosen, B., Lubinski, J., Domchek, S., Kauff, N. D., Lynch, H. T., Isaacs, C., Tung, N., Sun, P., & Narod, S. A. (2009). Tamoxifen and the risk of ovarian cancer in BRCA1 mutation carriers. *Gynecologic Oncology, 115*, 135–137.

Vogel, V. G., Costantino, J. P., Wickerham, D. L., Cronin, W. M., Cecchini, R. S., Atkins, J. N., Bevers, T. B., Fehrenbacher, L., Pajon, E. R., Jr., Wade, J. L., 3rd, Robidoux, A., Margolese, R. G., James, J., Lippman, S. M., Runowicz, C. D., Ganz, P. A., Reis, S. E., McCaskill-Stevens, W., Ford, L. G., Jordan, V. C., & Wolmark, N. (2006). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA, 295*, 2727–2741.

Vogel, V. G., Costantino, J. P., Wickerham, D. L., Cronin, W. M., Cecchini, R. S., Atkins, J. N., Bevers, T. B., Fehrenbacher, L., Pajon, E. R., Wade, J. L., 3rd, Robidoux, A., Margolese, R. G., James, J., Runowicz, C. D., Ganz, P. A., Reis, S. E., McCaskill-Stevens, W., Ford, L. G., Jordan, V. C., & Wolmark, N. (2010). Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer Prevention Research, 3*, 696–706.

https://doi.org/10.1375/twin.14.2.111 Published online by Cambridge University Press