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ORIGINAL PAPER

Infertility, treatment of infertility, and the risk of breast cancer among women with *BRCA1* and *BRCA2* mutations: a case–control study

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Abstract
Background Women with a breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*) mutation are at increased risk for developing breast and ovarian cancer. Various reproductive and hormonal factors have been shown to modify the risk of breast cancer. These studies suggest that estrogen exposure and deprivation are important in the etiology of hereditary cancer. Many patients are interested in the possibility of an adverse effect of fertility treatment on breast cancer risk. It

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is important to evaluate whether or not infertility per se or exposure to fertility medications increase the risk of breast cancer in genetically predisposed women.

Methods We conducted a matched case–control study of 1,380 pairs of women with a *BRCA1* or *BRCA2* mutation to determine if a history of infertility, the use of fertility medications, or undergoing in vitro fertilization (IVF) were associated with and increased the risk of breast cancer.

Results Sixteen percent of the study subjects reported having experienced a fertility problem and 4% had used a fertility medication. Women who had used a fertility medication were not at significantly increased risk of breast cancer (odds ratio [OR] = 1.21; 95% confidence interval [CI] = 0.81–1.82) compared to non-users. Furthermore, there was no risk associated with a history of use of a fertility medication when the subjects were stratified by parity: (OR = 1.29; 95% CI = 0.83–2.01 for nulliparous women and OR = 0.81; 95% CI = 0.30–2.22 for parous women).

Conclusions The results of this study suggest that the use of fertility medications does not adversely affect the risk of breast cancer among *BRCA* mutation carriers. Given the small sizes of the exposed subgroups, these findings should be interpreted with caution and confirmatory studies are required.

Keywords *BRCA1* · *BRCA2* · Infertility · Fertility treatment · In vitro fertilization · Breast cancer · Case–control study

Abbreviations

BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
IVF	In vitro fertilization
OR	Odds ratio
CI	Confidence interval

Introduction

Among the risk factors for breast cancer are hormonal and reproductive factors, such as parity and the age at first full-term birth. Early menarche and late menopause are both associated with a high number of lifetime ovulatory cycles, prolonged exposure to ovarian hormones (specifically estrogen and progesterone), and an elevated breast cancer risk [1–3]. Because drugs used to treat infertility stimulate ovulation, there is interest as to whether or not fertility treatments, which cause short-term elevations in ovarian steroid hormone levels, increase the risks of breast or ovarian cancer. Numerous studies have investigated the impact of infertility and fertility treatments on cancer risk in the general population. There appears to be no significant increase in breast cancer risk with exposure to fertility medication in the population at large (reviewed in [4–6]).

Women who inherit a deleterious mutation in either of the two breast cancer susceptibility genes, breast cancer

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susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*), face a lifetime risk of breast cancer that is ~10 times greater than the risk among women in the general population [7–10]. Studies of these high-risk women suggest that reproductive factors may be implicated in the etiology of their disease (reviewed in [11]). It is important to determine whether or not drugs that induce ovulation (fertility drugs) may increase cancer risk in mutation carriers. The objectives of the current study are twofold: first, to evaluate whether infertility per se is a risk factor for breast cancer and second, to determine whether the use of fertility medication or undergoing in vitro fertilization (IVF) is associated with an increased risk of breast cancer in *BRCA* mutation carriers.

Materials and methods

Study population and design

Eligible study subjects included living women who were identified at one of 47 participating centers in nine countries. These women were participants in ongoing research or clinical research protocols at the host institutions. These women sought testing of *BRCA1* and *BRCA2* mutations because of a personal or family history of breast or ovarian cancer. Study subjects were recruited between 1994 and 2007. All study subjects (with the exception of some of those from the University of Utah and the University of California Irvine) received genetic counseling.

The institutional review boards of the host institutions approved the study. All subjects provided written informed consent. In most cases, testing was initially offered to women who had been previously diagnosed with breast or ovarian cancer. When a *BRCA1* or *BRCA2* mutation was identified in a proband or her relative, genetic testing was offered to other at-risk individuals in the family. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. A woman was eligible for the current study when the molecular analysis established that she was a carrier of a deleterious mutation in the *BRCA1* or *BRCA2* gene. Most (>95%) of the mutations identified in the study subjects were either nonsense mutations, deletions, insertions, or small frameshifts resulting in a premature termination of protein translation.

Information was available on cancer status and reproductive history for a total of 7,742 women who carried a *BRCA1* or *BRCA2* mutation. Case subjects were study subjects with a diagnosis of invasive breast cancer. Control subjects were women who never had breast cancer and who were also carriers of a mutation in *BRCA1* or *BRCA2*. Potential subjects were excluded if they had been diagnosed with ovarian cancer (1,171 women) or another cancer (110 women) prior to the year of breast cancer diagnosis of the case. Patients were also excluded if they had a bilateral mastectomy (254 women), or if pertinent information was missing (1,188 women). After exclusions, there was a total of 4,994 eligible women, including 2,577 women with breast cancer (potential case subjects) and 2,417 women without breast cancer (potential controls). On average, 6.5 years had elapsed between the age at diagnosis and the age at interview. For 1,090 cases (79%), the time between diagnosis and questionnaire completion exceeded 1 year (prevalent cases). A single control subject was selected for each case subject, matched according to mutation in the same gene (*BRCA1* or *BRCA2*), year of birth (within 1 year), country of residence and parity (ever/never; including live-born and still-born), resulting in a total of 1,380 matched case–control pairs, including 175 nulliparous and 1,205 parous pairs of women. Of the 1,380 pairs used in the analyses, in five pairs the case and matched control were from the same family.

Data collection

Case and control subjects completed a questionnaire that asked for information regarding family history, reproductive and medical histories, and selected lifestyle factors, including smoking and the use of oral contraceptives. Questionnaires were administered at the individual centers at the time of a clinic appointment or at their home at a later date. The following three questions were of particular interest for the current study: (1) have you ever seen a doctor for a problem of difficulty in getting pregnant or in carrying a pregnancy, such as several miscarriages? (yes/no); (2) have you ever taken any medication to increase your chances of becoming pregnant (yes/no) and; (3) have you ever received fertility treatment such as IVF/embryo transfer to help you get pregnant? The types of fertility medication and the specific treatments were also collected.

Statistical methods

A matched case–control analysis was performed to evaluate the associations between a history of infertility, use of fertility medication or fertility treatment, and the risk of breast cancer. Use of fertility medication was censored one calendar year prior to the breast cancer diagnosis of the matched case. The Student's *t*-test was used to compare continuous variables and the chi-square test was used to test for differences in categorical variables. Conditional logistic regression was used to estimate the univariate odds ratios (OR) and 95% confidence intervals (CI) for breast cancer associated with a history of infertility.

To separate the effects of fertility per se versus treatment for infertility, the analyses were first conducted in all the subjects combined, and then separately for the subgroups of parous and nulliparous women. Parity was defined at the time of completion of the research questionnaire and not at the time at which fertility treatment was received. A multivariate analysis was carried out to control for the potential confounding effects of age at menarche and ethnicity (white, French-Canadian, Jewish, and other). Similar analyses were carried out to test for an association with the use of fertility medication, or undergoing IVF treatment. All statistical tests were twosided. All analyses were performed using the SAS statistical package, version 9.1.3 (SAS Institute, Cary NC).

Results

Subject characteristics are presented in Table 1. There were 1,380 matched sets, including 1,205 sets of parous women and 175 sets of nulliparous women. Seventy-six percent of the pairs had a *BRCA1* mutation and 24% of the pairs had a *BRCA2* mutation. Case and control subjects were similar with respect to age and oral contraceptive use. Case subjects had an earlier age at menarche compared with the control subjects (12.9 vs. 13.0 years; $p = 0.003$). Because there was a difference in the distribution of the ethnicity of the study subjects ($p = 0.004$) we adjusted for ethnicity in the multivariate analysis.

Sixteen percent of all the study subjects reported having experienced a fertility problem. Among the 437 women who reported a fertility problem, 14% were nulliparous at the time of completion of the questionnaire. Four percent of the study subjects reported having used a fertility medication and one percent had received IVF treatment (Table 2). Data regarding the type of fertility medication were available for 87 of the 117 study subjects who reported taking a medication (74%). The frequencies were as follows: 44% clomiphene citrate-containing (i.e., clomid), 22% gonadotropin-containing (i.e., pergonal), 8% other (bromocriptine, mixture of various drugs, estrogen), and 26% unknown or missing.

Among all the women, the proportions of cases and controls ever having reported a fertility problem, using a fertility medication, or undergoing IVF treatment were similar ($p > 0.10$ for all comparisons) (Table 2). There was

Table 1 Characteristics of case and control subjects

Variables	Control subjects $n = 1{,}380$	Cases subjects $n = 1{,}380$	p[a]
Date of birth, mean (range)	1955.5 (1916–1979)	1955.2 (1916–80)	0.42
Current age, mean (range)	46.2 (21–83)	46.0 (18–82)	0.63
Mutation, *n* (%)			
BRCA1	1,054 (76.4)	1,054 (76.4)	N/A
BRCA2	326 (23.6)	326 (23.6)	
Age at menarche, mean	13	12.9	0.003
Oral contraceptive use, *n* (%)			
Never	473 (34.4)	495 (36.0)	0.37
Ever	902 (65.6)	879 (64.0)	
Missing	5	6	
Ethnicity, *n* (%)			
Other white	925 (67.1)	966 (70.0)	0.004
Jewish	315 (22.8)	248 (18.0)	
French Canadian	118 (8.6)	129 (9.4)	
Other	22 (1.6)	37 (2.7)	
Country of residence, *n* (%)			
Canada	442 (32.0)	442 (32.0)	N/A
United States	434 (31.5)	434 (31.5)	
Poland	351 (25.4)	351 (25.4)	
Israel	76 (5.5)	76 (5.5)	
Norway	37 (2.7)	37 (2.7)	
Austria	18 (1.3)	18 (1.3)	
Italy	12 (0.9)	12 (0.9)	
United Kingdom	5 (0.4)	5 (0.4)	
Sweden	5 (0.4)	5 (0.4)	

[a] All *p*-values are univariate and were derived using the Student's *t*-test for continuous variables and the χ^2 test for categorical variables

N/A, Not applicable. Country of residence was that at the time of testing

Table 2 Fertility problem, use of a fertility medication, or IVF treatment and the risk of breast cancer in case and control subjects, in all subjects and stratified by parity

Variables	Controls $n = 1{,}380$	Cases $n = 1{,}380$	p
Fertility problem, *n* (%)			
All ($n = 1{,}380$)			
Never	1,147 (83.1)	1,176 (85.2)	0.14
Ever	233 (16.9)	204 (14.8)	
Parous[a] ($n = 1{,}205$)			
Never	1,008 (83.7)	1,028 (85.3)	0.28
Ever	197 (16.4)	177 (14.7)	
Nulliparous ($n = 175$)			
Never	139 (79.4)	148 (84.6)	0.28
Ever	36 (20.6)	27 (15.4)	
Fertility medication, *n* (%)			
All ($n = 1{,}380$)			
Never	1,294 (95.9)	1,305 (95.5)	0.76
Ever	56 (4.2)	61 (4.5)	
Missing[b]	30	14	
Parous ($n = 1{,}205$)			
Never	1,137 (96.0)	1,139 (95.0)	0.58
Ever	47 (4.0)	54 (4.5)	
Missing	21	12	
Nulliparous ($n = 175$)			
Never	157 (94.6)	166 (96.0)	0.8
Ever	9 (5.4)	7 (4.1)	
Missing	9	2	
IVF treatment, *n* (%)			
All ($n = 1{,}380$)			
Never	1,305 (99.2)	1,308 (99.3)	0.99
Ever	11 (0.8)	9 (0.7)	
Missing[b]	64	63	
Parous ($n = 1{,}205$)			
Never	1,145 (99.4)	1,143 (99.4)	0.99
Ever	7 (0.6)	7 (0.6)	
Missing	53	55	
Nulliparous ($n = 175$)			
Never	160 (97.6)	165 (98.8)	0.69
Ever	4 (2.4)	2 (1.2)	
Missing	11	8	

[a] Parous includes live born and still born

[b] Missing data were excluded in the Student's *t*-test. *p*-values are based on McNemar test

no association between a history of infertility (OR = 0.88; 95% CI = 0.72–1.09), or the use of fertility medication (OR = 1.21; 95% CI = 0.81–1.82) or IVF treatment (OR = 0.98; 95% CI = 0.39–2.45), and the risk of breast cancer among the parous and nulliparous women combined (Table 3). Stratifying by mutation status or parity did not substantially affect these results.

Because clomiphene citrate- and gonadotropin-containing medications were the most commonly used types of fertility drugs in these study subjects, we also evaluated breast cancer risk associated with the use of these two drugs (Table 4). In all the study subjects combined, the odds ratios for use of clomiphene-containing fertility medication was 0.96; 95% CI = 0.54–1.72; $p = 0.89$. The odds ratio for the use of a gonadotropin-containing drug was 2.32 (95% CI = 0.91–5.95; $p = 0.08$), but few subjects were exposed and this association did not achieve statistical significance.

Discussion

The results of this study suggest that among women with a *BRCA* mutation, the use of a fertility medication does not increase the risk of breast cancer. This was observed in all the study subjects combined, as well as in subgroups defined by mutation status and parity. We observed a possible adverse effect among women who used gonadotropin-containing fertility medications. This effect is unlikely to be attributed to fertility per se; a fertility problem was not a risk factor and the results for the gonadotropins were similar among parous and nulliparous women (data not shown). There was no increased risk associated with the use of drugs that contained clomiphene citrate. Additional studies with equally large samples are necessary to confirm our results.

In the general population, no consistent relationship between infertility and the risk of breast cancer has emerged [4–6]. Results from cohort studies have found that the incidence rates of breast cancer among infertile women are similar to the rates in fertile women. Similarly, findings from case–control studies have shown that a history of infertility is not associated with breast cancer risk. Furthermore, the use of fertility drugs does not appear to be associated with an increase in breast cancer risk (reviewed [5, 12]). In a recent meta-analysis by Salhab et al., the pooled relative risk (RR) associated with ovulation induction was 0.88 ($p = 0.2$) and 1.1 ($p = 0.3$) for IVF treatment [6]. The authors of one study reported a significant increase in breast cancer diagnosed within 12 months of exposure to fertility drugs with IVF (standardized incidence ratio = 2.0; 95% CI = 1.2–3.2) [5]. This may be relevant given that there is a transient increase in breast cancer diagnosis following a recent pregnancy [13, 14].

Few studies have evaluated infertility or fertility treatment among women with a family history of breast cancer [15–17]. In a large prospective cohort study, Gauthier reported that fertility treatment was associated with an increase in risk among women with a first-degree relative

Table 3 Association between a fertility problem, use of a fertility medication, or IVF treatment and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers, in all subjects and stratified by parity

	Univariate OR (95% CI)	*p*	Multivariate OR[a] (95% CI)	*p*
Fertility problem (ever vs. never)				
All subjects combined				
BRCA1 + *BRCA2*	0.85 (0.69–1.05)	0.13	0.88 (0.72–1.09)	0.23
BRCA1	0.86 (0.67–1.09)	0.20	0.89 (0.70–1.13)	0.34
BRCA2	0.84 (0.56–1.27)	0.41	0.92 (0.60–1.40)	0.69
Parous women				
BRCA1 + *BRCA2*	0.88 (0.70–1.10)	0.26	0.91 (0.72–1.14)	0.39
BRCA1	0.87 (0.68–1.13)	0.30	0.90 (0.70–1.17)	0.43
BRCA2	0.90 (0.56–1.42)	0.64	0.95 (0.58–1.54)	0.84
Nulliparous women				
BRCA1 + *BRCA2*	0.74 (0.37–1.47)	0.39	0.77 (0.37–1.61)	0.49
BRCA1	0.69 (0.30–1.62)	0.40	0.94 (0.37–2.44)	0.90
BRCA2	0.72 (0.42–1.23)	0.23	0.76 (0.43–1.33)	0.33
Fertility medication (ever vs. never)				
All subjects combined				
BRCA1 + *BRCA2*	1.10 (0.74–1.63)	0.64	1.21 (0.81–1.82)	0.36
BRCA1	1.09 (0.69–1.72)	0.73	1.22 (0.76–1.94)	0.41
BRCA2	1.13 (0.52–2.46)	0.75	1.25 (0.56–2.78)	0.59
Parous women				
BRCA1 + *BRCA2*	1.18 (0.76–1.81)	0.46	1.29 (0.83–2.01)	0.26
BRCA1	1.10 (0.67–1.80)	0.71	1.20 (0.72–1.98)	0.48
BRCA2	1.48 (0.60–3.63)	0.40	1.77 (0.67–4.68)	0.25
Nulliparous women				
BRCA1 + *BRCA2*	0.79 (0.29–2.09)	0.62	0.81 (0.30–2.22)	0.68
BRCA1	1.00 (0.29–3.45)	1	1.21 (0.34–4.32)	0.77
BRCA2	0.50 (0.09–2.73)	0.42	0.64 (0.11–3.72)	0.62
IVF treatment (ever vs. never)				
All subjects combined				
BRCA1 + *BRCA2*	0.90 (0.37–2.22)	0.82	0.98 (0.39–2.45)	0.97
BRCA1	0.88 (0.32–2.41)	0.8	0.99 (0.35–2.76)	0.98
BRCA2	1.00 (0.14–7.10)	1.00	0.88 (0.12–6.52)	0.90
Parous women				
BRCA1 + *BRCA2*	1.17 (0.39–3.47)	0.78	1.23 (0.41–3.69)	0.72
BRCA1	1.25 (0.34–4.65)	0.74	1.30 (0.35–4.92)	0.69
BRCA2	1.00 (0.14–7.10)	1	0.95 (0.13–7.10)	0.96
Nulliparous women				
BRCA1 + *BRCA2*	0.50 (0.09–2.73)	0.42	0.85 (0.14–5.09)	0.86
BRCA1	0.50 (0.09–2.73)	0.42	0.95 (0.16–5.78)	0.95
BRCA2	N/A	N/A	N/A	N/A

[a] ORs and 95% CI adjusted for age at menarche and ethnicity

with breast cancer (RR = 1.4; 95% CI = 1.0–1.9) compared to untreated women with a first-degree relative with breast cancer. No significant association was observed among women without a family history [17]. *BRCA* mutation analysis was not performed and the sample of women with a family history was small ($n = 32$ cases). Two other studies have reported that a family history does not seem to modify the association between infertility and breast cancer risk [15, 16].

BRCA-associated breast cancers appear to be influenced by various reproductive and hormonal factors; however, the risk factor profiles differ for *BRCA1* and *BRCA2* mutation carriers (reviewed in [11]). Both oophorectomy [18] and the use of tamoxifen [19] protect against breast cancer among carriers of either type of mutation. The use of oral contraceptives protects against ovarian cancer, with little influence on breast cancer risk (reviewed in [11]). Among women with a *BRCA1* mutation, a late age at

Table 4 Association between use of clomiphene citrate-containing or gonadotropin-containing fertility medication and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers, in all subjects

	Controls, *n*	Cases, *n*	Univariate OR (95% CI)	*p*	Multivariate OR[a] (95% CI)	*p*
Never users	1,294	1,305	1.00 (referent)	N/A[b]	1.00 (referent)	N/A
Clomiphene citrate-containing	27	24	0.90 (0.51–1.61)	0.7	0.96 (0.54–1.72)	0.89
Gonadotropin-containing	10	16	1.84 (0.73–4.62)	0.19	2.32 (0.91–5.95)	0.08

[a] ORs and 95% CI adjusted for age at menarche and ethnicity

[b] Not applicable

menarche and breastfeeding are protective [20, 21]. Risk increases with increasing parity among *BRCA2* mutation carriers [22].

Based on this body of evidence, we hypothesized that transient exposure to exogenous gonadal hormones or to high levels of endogenous hormones might result in an increase in the risk of breast cancer. Fertility treatment is usually associated with increases in circulating endogenous estrogen and progesterone. There is concern that supra-physiologic increases in these hormones might be mitogenic in the breast and that prolonged exposure may increase breast cancer risk by stimulating breast epithelial proliferation [23, 24].

We were not able to evaluate the breast cancer risk according to the cause of infertility; however, we were able to restrict our analysis to use of drugs that contained clomiphene or gonadotropins (both of which are commonly prescribed to women with ovulatory disorders). We saw no association with the use of clomiphene citrate which is a selective estrogen receptor modulator, is structurally and functionally similar to tamoxifen, and exhibits both agonist or antagonist effects, depending on the tissue [25], and this drug may act as an antiestrogen in the mammary epithelium [26]. Other reports have shown a protective effect of fertility medication. In a large prospective analysis of the Nurses' Health Study II, Terry et al. recently reported an inverse association between infertility due to an ovulatory disorder and breast cancer risk [27]. There was a 40% decrease in the incidence of breast cancer among women with ovulatory infertility who used ovulation-induction therapy, compared to women with no reported problem (hazard ratio (HR) = 0.60; 95% CI = 0.42–0.85). In contrast, an increase in breast cancer risk was observed among women with ovulatory infertility who did not receive ovulation induction (HR = 1.4; 95% CI = 0.97–2.0). In a large case–control study, Rossing et al. reported a non-significant decreased risk of breast cancer among infertile women who used clomiphene, compared with infertile women who had not used this drug (RR = 0.5; 95% CI = 0.2–1.2) [28].

We observed that the use of gonadotropin-containing fertility medication was associated with an increased risk of breast cancer compared with never users (OR = 2.32; 95% CI = 0.91–5.95; $p = 0.08$) although this association did not achieve statistical significance. In a large case–control study, Burkman et al. reported a two- to threefold increased risk of breast cancer among women who used gonadotropins for 6 months or more or for at least six cycles [29]. Gonadotropin-containing fertility medications usually contain FSH or LH alone or in combination and act by directly stimulate the ovaries resulting in estrogen and progesterone levels that are much higher that what is observed during a normal menstrual cycle [30, 31]. Due to the high levels of hormones induced by gonadotropins, the safety of these preparations should be addressed in future studies of high risk women.

This is the only study to date looking at a role of infertility or fertility treatment specifically among *BRCA* mutation carriers. Our results were limited by the small proportion of women who had ever used a fertility medication or who had received fertility treatment. Four percent of the study subjects had used fertility medication, and only 1% of the women had undergone IVF treatment. Thus, there was limited power to detect an effect of IVF treatment because this exposure was rare. Following stratification by mutation status and parity, the subgroups were small. Also, we were unable to evaluate the effect of different causes of infertility (ovulatory, tubal, cervical, or male factors) on breast cancer risk due to the lack of these details. Information regarding specific fertility medication was missing for 27% of the study subjects. The history of fertility medication was based on subject reporting and was not confirmed by review of medical records. One of our primary variables of interest was history of fertility problem. We restricted this to problems which lead to a medical consultation in order to enhance the objectivity of the response. However, it is of course possible that there were additional women who experienced infertility but did not seek medical care.

Our data were based on self-reporting by subjects; this may have introduced recall bias if the case subjects more likely to report usage than the controls. However, this is unlikely given that we found no significant difference in the proportion of women who reported a history of infertility, use of fertility medication, or fertility treatment among the parous women. We included prevalent cases; if

the effect of prior fertility treatment leads to an effect on mortality after the diagnosis of breast cancer, this selection may introduce survivorship bias. Additional studies with a more detailed collection of the type, dose, and time-course of fertility treatment are warranted. Furthermore, due to changes in fertility treatments over time, a distinction between past and recent treatment should be investigated. Because a BRCA mutation also confers a high lifetime risk of ovarian cancer [7], the effect of fertility treatment on ovarian cancer risk also requires evaluation.

Conclusions

In summary, infertility or its treatment do not appear to increase the risk of breast cancer in women with a *BRCA1* or *BRCA2* mutation. We believe that the treatment of infertility is not contra-indicated for *BRCA* mutation carriers. The possible adverse relationship with the use of gonadotropins warrants further study.

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