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# Outcomes of Primary Surgical Cytoreduction in Patients with *BRCA*-associated High-grade Serous Ovarian Carcinoma

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## Abstract

**Objective—***BRCA*-associated and sporadic ovarian cancers have different pathologic and clinical features. Our goal was to determine if *BRCA* mutation status is an independent predictor of residual tumor volume following primary surgical cytoreduction.

**Methods—**We conducted a retrospective analysis of patients with FIGO stage IIIC-IV high-grade serous ovarian cancer classified for the presence or absence of germline *BRCA* mutations. The primary outcome was tumor-debulking status categorized as complete gross resection (0mm), optimal but visible disease (1-10mm), or suboptimal debulking (>10mm) following primary surgical cytoreduction. Overall survival by residual tumor size and *BRCA* status was also assessed as a secondary endpoint.

**Results—**Data from 367 patients (69 *BRCA* mutated, 298 *BRCA* wild-type) were analyzed. Rate of optimal tumor debulking (0-10mm) in *BRCA* wild-type and *BRCA*-mutated patients were 70.1% and 84.1%, respectively ($P$=0.02). On univariate analysis, increasing age (10-year OR, 1.33; 95% CI, 1.07–1.65; $P$=0.01) and wild-type BRCA status (OR, 0.47; 95% CI, 0.23–0.94, $P$=0.03) were both significantly associated with suboptimal surgical outcome. On multivariate analysis, *BRCA* mutation status was no longer associated with residual tumor volume (OR, 0.63; 95% CI, 0.31–1.29; $P$=0.21) while age remained a borderline significant predictor (10-year OR, 1.25; 95% CI, 1.01–1.56; $P$=0.05). Both smaller residual tumor volume and mutant *BRCA* status were significantly associated with improved overall survival.

**Conclusion—***BRCA* mutation status is not associated with the rate of optimal tumor debulking at primary surgery after accounting for differences in patient age. Improved survival of *BRCA* carriers is not the result of better surgical outcomes but instead intrinsic tumor biology.

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## Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer in the United States, accounting for approximately 22,000 new diagnoses and 15,000 deaths annually [1]. The standard of care for patients with advanced (stage III/IV) ovarian cancer is primary surgical cytoreduction followed by platinum-based chemotherapy. Several pooled analyses of clinical trials for newly diagnosed advanced ovarian cancer have found that age, histology, performance status, and residual tumor size after surgical cytoreduction are independent prognostic factors [2-5]. It is now also known that approximately 8-13% of unselected ovarian cancers, and 15-17% of the high-grade serous subtype, are associated with germline *BRCA1* or *BRCA2* mutations [6,7]. Several studies have found that germline *BRCA1/2* status is also a powerful predictor of survival [8-11], independent of traditional prognostic factors such as platinum-sensitivity [12]. *BRCA1/2*-associated ovarian cancers may also have distinct patterns of recurrence following primary therapy [13]. However, it is unclear if higher rates of optimal surgical cytoreduction may be a contributing factor in the improved overall survival seen in BRCA-associated ovarian cancer.

The underlying biologic differences of *BRCA*-associated ovarian cancers may also affect the outcome of primary surgical cytoreduction through differences in micro-invasiveness or pattern of spread. Comprehensive pathologic reviews of *BRCA1/2*-associated ovarian cancers have shown that they are more likely than age-matched sporadic controls to be of serous histology, to be high grade, and to stain strongly for *TP53* [14,15]. Review of tumor morphology, necrosis, and mitotic index in sporadic and BRCA-associated ovarian cancers also reveal important differences. In a recent study, tumor-infiltrating lymphocytes, high mitotic index, solid, pseudoendometrioid, and transitional cell carcinoma-like features, pleomorphism, and necrosis were seen more frequently in BRCA1-associated cases than controls [16]. These observations raise the possibly that germline *BRCA* mutations may affect the results of surgical cytoreduction.

We investigated the association between germline *BRCA1/2* mutations in serous ovarian cancers and the outcome of primary surgical cytoreduction. Data from a single center and The Cancer Genome Atlas (TCGA) were pooled. Our goal was to determine if *BRCA*-associated ovarian cancers have different rates of complete and optimal debulking compared to sporadic ovarian cancers.

## Methods

### Patients

After Institutional Review Board/Privacy Board (IRB/PB) approval, two cohorts of patients were ascertained.

The first cohort (“MSKCC Cohort”) was composed of patients identified from a prospectively maintained institutional database. Patients had International Federation of Gynecology and Obstetrics (FIGO) stage IIIC–IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma and had primary surgical cytoreduction at Memorial Sloan-Kettering Cancer Center (MSKCC) between January 1, 2001 and January 31, 2010. All patients in the current analysis also had *BRCA* mutation testing on one of two IRB-approved prospective studies conducted by the Clinical Genetics Service to investigate the clinical significance of germline *BRCA* mutations. Details of these two follow-up studies have been published previously.[17] During the study period, patients presenting for treatment of newly diagnosed pelvic serous cancer were not required to undergo genetic counseling or testing. Between 2001 and 2008 patients were typically referred based on at least one of the following: 1) family history of breast cancer prior to age 50 or ovarian cancer at any age in a

first or second degree relative, 2) Eastern European (Ashkenazi) Jewish heritage 3) patient request, or 4) physician request. Since July 2008, genetic counseling has been offered to (but not required of) all patients diagnosed with high-grade serous ovarian cancer irrespective of family history. Patients tested for *BRCA* germline mutations beyond 24 months of diagnosis were also excluded from analysis to minimize the selection bias that could result from including patients referred for genetic testing because of prolonged survival. All *BRCA1* and *BRCA2* mutations were predicted to be deleterious. Patients with variants of unknown significance were considered to be *BRCA*-negative. Patients were excluded if they received neoadjuvant chemotherapy prior to attempted cytoreductive surgery, had non-serous histology, or had low-grade disease (low-malignant potential or grade 1). Demographics including age at diagnosis, FIGO stage, and histologic grade. Operative notes were reviewed to determine the volume of residual disease. All patients received platinum-based cytotoxic chemotherapy as per appropriate institutional protocol at time of diagnosis. Overall survival was calculated from date of diagnosis to date of death or last follow-up.

The second cohort ("TCGA Cohort") was obtained from The Cancer Genome Atlas (TCGA) publication on ovarian cancer and through the TCGA Data Portal (http://cancergenome.nih.gov/). TCGA is a clinically annotated collection of untreated high-grade serous ovarian cancer specimens selected to have greater than 70% tumor cell nuclei and less than 20% necrosis. All patients received a platinum agent, and 94% received a taxane after cytoreduction. Only samples from patients with FIGO stage IIIC–IV disease, those with recorded volume of residual disease, and those sequenced by TCGA were included in this analysis. Because MSKCC contributed tumor samples to TCGA, patients included in the MSKCC cohort were excluded from the TCGA cohort to prevent duplicates. The sequencing methods used in TCGA have been described previously [18]. For the purposes of this analysis, only germline *BRCA1/2* mutations were considered. Tumors with somatic *BRCA1/2* mutations were analyzed as *BRCA* wild type because the clinical significance of somatic mutations is unclear and to be consistent with the MSKCC cohort for which only germline mutation testing was performed. Data was current as of August 25, 2010.

### Statistical Methods

This was a pooled retrospective analysis with the primary objective of determining the rate of optimal debulking in patients following primary cytoreduction by *BRCA* status (*BRCA1/2*+, *BRCA*−). The associations between clinical factors and *BRCA* status were tested by either Pearson chi-square, Fisher's-exact test for categorical variables, or ANOVA for continuous variables. All *P*-values reported are two-sided. Univariate and multivariate analyses for age, stage, grade, and *BRCA* mutation status were performed using binary logistic regression, with optimal debulking (0-10 mm) and suboptimal debulking (>10 mm) as the dependent variables. For these analyses, suboptimal debulking was used as the reference outcome. Overall survival (OS) was calculated from the date of primary cytoreduction surgery to death or last follow-up. Univariate OS analyses were performed, stratifying for debulking and *BRCA* status. OS rate was estimated using Kaplan–Meier method. *P*-values were obtained by log-rank test. Variables were regarded as significant at $P<0.05$. To build the multivariate model a forward selection technique was employed using a significance level of 0.10 for the variable to remain in the model [19]. Analyses were conducted using SPSS version 19 (SPSS, Chicago, IL).

## Results

### Surgical Outcomes

The baseline demographics of the two cohorts are shown in Tables 1 and 2. In both cohorts, patients with and without deleterious *BRCA* mutations were well balanced with regards to

stage and grade. As has been described previously, patients with *BRCA1/2* mutations were on average approximately 6 years younger at the age of diagnosis than patients without mutations.[9] The overall debulking rate (0-10 mm) was 93.7% in the MSKCC cohort and 75.7% in the TCGA cohort. When surgical outcome was broken out in three groups (0mm, 1-10mm, >10mm), there were significant differences in surgical outcomes in the MSKCC, but not the TCGA, cohort. Surgical outcomes were also explored by type of *BRCA* mutation (*BRCA*−, *BRCA1*, and *BRCA2*) as shown in Table 3. No differences in surgical outcomes were observed regardless of whether completely resected patients (0 mm) were included in the optimal debulking category or analyzed separately.

A univariate analysis of surgical outcomes of the combined MSKCC and TCGA cohorts is shown in Table 4. In this analysis, stage was not associated with debulking status. Both age (10-year OR, 1.33; 95% CI, 1.07-1.65, $P = 0.01$) and BRCA mutations (OR, 0.47, 95% CI, 0.23-0.94, $P = 0.03$) were significantly associated with surgical outcomes. Finally, patient cohort significantly predicted surgical outcome (OR, 0.41; 95% CI, 0.23-0.74; $P = 0.01$). A multivariate analysis of surgical outcomes incorporating age at diagnosis, patient cohort, and *BRCA* mutation status is shown in Table 5. In this multivariate model, age (10-year OR, 1.25; 95% CI, 1.01-1.56; $P=0.05$) and patient cohort (OR, 0.47; 95% CI, 0.25–0.85; $P=0.01$) maintained at least borderline significance. *BRCA* mutation status, however, was not associated with surgical outcome (OR, 0.63; 95% CI, 0.31-1.29; $P=0.21$).

### Survival

During the period of follow-up, 208 deaths were observed in the total cohort of 365 patients. Median follow-up time for the entire cohort was 31.2 months, and 27.4 months for patients still alive. Figure 1A depicts the Kaplan-Meier overall survival curves by surgical outcome. Median overall survival was 59.1 months (0 mm), 39.3 months (1-10 mm), and 34.2 months (>10 mm). These differences were significant (*P* value for group 0.01). Figure 1B depicts the Kaplan-Meier overall survival curves by *BRCA* status. Median overall survival was 60.0 months for patients with *BRCA1/2* mutations, and 40.3 months for patients without *BRCA1/2* mutations ($P <0.001$).

## Discussion

Our data suggest that women with *BRCA1/2*-associated and sporadic ovarian cancer have similar rates of optimal debulking (0-10mm) following primary surgical cytoreduction. Although our univariate analysis suggested *BRCA1/2*-mutated patients had smaller residual tumor volumes, this effect was no longer observed after controlling for differences in surgical outcome by age. These data suggest that any improvement in surgical outcome observed in *BRCA1/2*-mutated patients may be the result of the younger age at which these patients develop ovarian cancer.

Our analysis grouped patients with complete gross resection (0 mm) and optimal but visible disease (1-10 mm) in order to improve the power of the multivariate analysis to detect differences in surgical outcome. However, BRCA status remained a non-significant predictor of residual tumor volume when patients with complete gross resection were compared to patients with any visible disease (data not shown).

Age is proven to be a reliable predictor of poorer outcome in advanced ovarian cancer [4], but it is unclear if there is a direct association between older patients and inferior surgical outcomes. It is possible that surgeons are willing to undertake a more aggressive operative approach in younger patients in order to achieve optimal cytoreduction. However, when comparing the older and younger half of the 85 patients in the MSKCC cohort with residual tumor volumes of 0-10 mm, no differences in the rate of bowel resection, ostomy creation,

splenectomy, distal pancreatectomy, or diaphragm resection were observed. This suggests that younger patients did not, on average, require more procedures in order to achieve an optimal debulking. If younger patients have better operative outcomes because their surgeons are willing to be more aggressive, one might expect this to be reflected in the number or type of procedure undertaken in these patients. Detailed surgical reports on patients in the TCGA cohort were not available. Few previous studies have specifically examined the effect of increasing age on the outcome of primary surgical cytoreduction. In one series of 360 consecutive patients who underwent primary surgery for ovarian cancer, age was a significant predictor of residual tumor size on univariate, but not multivariate, analysis [20]. In another multicenter study examining the ability of preoperative computed tomography to predict optimal tumor debulking, no age-dependent differences were seen [21].

Our study also did not find differences in surgical outcome in patients with FIGO stage III or stage IV disease. Although it is possible this is due to the small number of stage IV patients (14.8%) in the combined cohort, it is more likely that our exclusion of patients who had neoadjuvant chemotherapy explains this finding. Neoadjuvant chemotherapy followed by interval surgical cytoreduction is an accepted standard of care in patients with clearly unresectable stage IV disease [22]. We chose, however, to exclude patients who received neoadjuvant chemotherapy for several reasons. First, there are many unmeasurable factors that influence a gynecologic oncologist's decision to pursue this treatment strategy. Second, patients who have a suboptimal response to neoadjuvant chemotherapy are often never taken for interval cyctoreduction. Finally, the TCGA cohort excluded patients who received neoadjuvant chemotherapy and including these patients in the MSKCC cohort would introduce potential biases. As a result, the stage IV patients in this study were heavily enriched for patients with lower volume, or more resectable, disease.

Our analysis has several important strengths. Our combined cohort of 367 patients, including 69 with deleterious *BRCA1/2* mutations, is fairly large given the relative rarity of *BRCA1/2* mutations. Moreover, all patients had high-grade (FIGO Grade 2 or 3) serous cancer. Because histology and possibly grade may influence cytoreducibility and are also related to *BRCA* status, this restriction minimizes another source of potential confounding [23]. Our analysis includes patients from 15 different high-volume surgical centers staffed by experienced gynecologic oncology surgeons. Surgeon experience and subspecialty training are both factors that are well known to influence the outcome of primary cytoreduction and, in fact, were observed in this study as well [24]. Combined with the fact that the rates of complete and optimal tumor debulking seen here are consistent with previously published rates, it is unlikely these finding are the result a particular set of surgical practices at a single institution or group of institutions.

The cohorts in this analysis were also crafted to limit ascertainment bias with respect to *BRCA* mutation status. The MSKCC cohort was limited to patients tested for *BRCA* mutations within 2 years of the initial diagnosis of ovarian cancer. This restriction, which caused us to remove 34 patients from the analysis, eliminated patients who may have been *BRCA* tested due to unexpected longevity. This is especially important as overall survival is also associated with residual tumor volume. The TCGA cohort was composed of entirely incident ovarian cancer cases selected on the basis of tissue availability that met TCGA requirements. Finally, the control patients in our analysis were all confirmed non-carriers rather than untested matched controls. Our decision to include MSKCC patients with variants of unknown significance (VUS) in the wild-type cohort could potentially bias our findings in favor of the null-hypothesis (ie-concluding there is no difference in optimal cytoreduction between BRCA mutant and wild-type patients) if these mutations were later determined to be deleterious. However, only one of the 69 wild-type MSKCC patients had a

VUS and a repeat analysis excluding this patient did not change our results or their significance levels (data not shown).

The clinical outcomes of patients included in our analysis provide further confidence that the cohort is representative of the larger ovarian cancer population. The significant differences in the median survival of patients who achieved complete, optimal, and suboptimal resection are consistent with previously published reports [5,25]. The median survival of patients with *BRCA*-associated ovarian cancer was better than that for sporadic ovarian cancers, consistent with prior studies [10,11]. There were significant differences in surgical outcomes in the MSKCC and TCGA cohorts. It is possible that these differences are the result of the tissue selection criteria use by the TCGA, which required banking of relatively large tumor specimens. This may have biased the TCGA cohort towards patients with greater disease burdens that were, therefore, less likely to be optimally debulked.

We found that despite previously established differences in the pathologic appearance and biologic behavior of *BRCA*-associated and sporadic ovarian cancers, the rate of primary optimal tumor debulking of these two entities was not significantly different. Our finding does not rule out the possibility that a much larger study might detect a small, but statistically significant, difference in surgical outcomes of these two groups. We conclude that the improved survival seen in ovarian cancer patients with germline BRCA mutations is unlikely explained by differences in surgical outcome.

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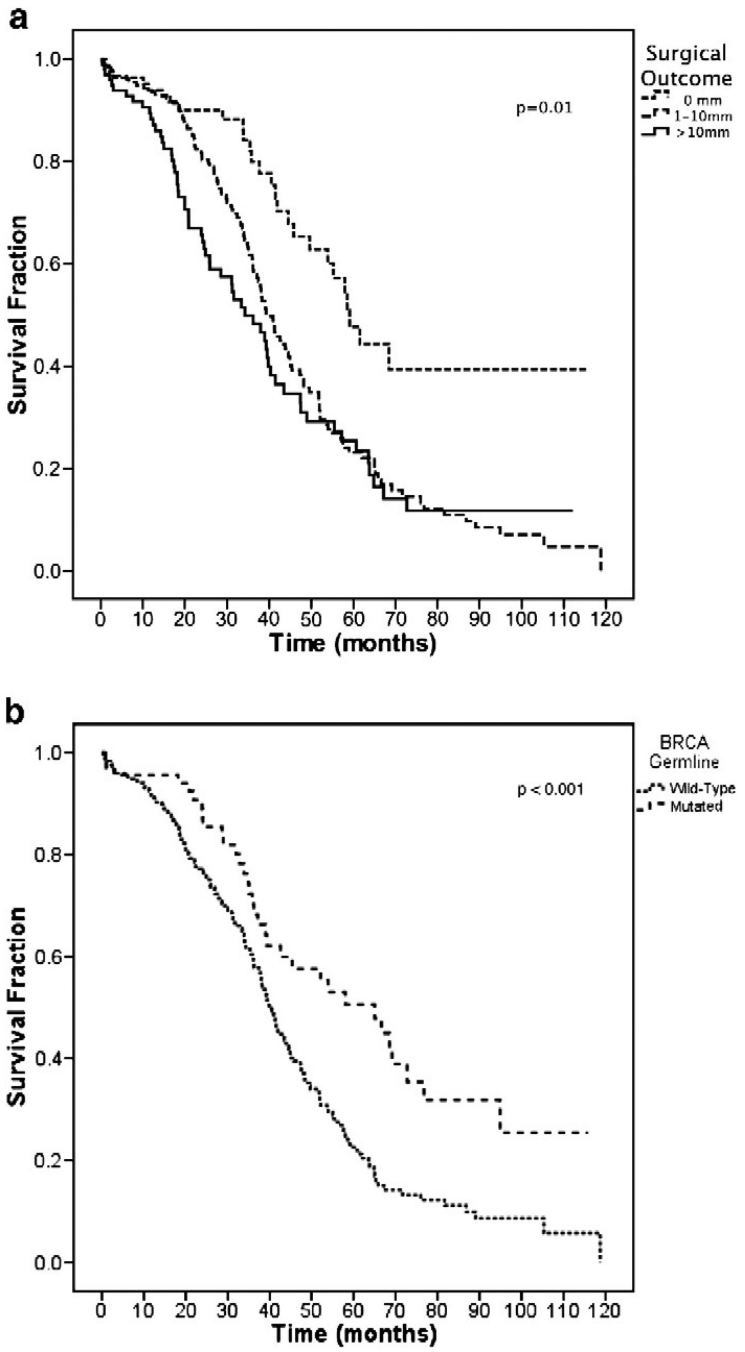


**Figure 1.**
Overall survival stratified by surgical outcome (A) and BRCA germline mutation (B).

**Table 1**

MSKCC Patient Baseline Demographics

| **Variables** | **All** | **BRCA (-)** | ***BRCA1/2* (+)** | ***P*-value*** |
|---|---|---|---|---|
| Whole Cohort | 101 | 69 | 32 | |
| Age | | | | |
| Median (mean) | 59.6 (58.5) | 62.1 (60.1) | 56.5 (55.1) | 0.01 |
| Range | 32.2 - 78.2 | 40.3 -78.2 | 32.2 - 74.0 | |
| Diagnosis | | | | |
| Ovarian | 78 (77.2%) | 50 (72.5%) | 28 (87.5%) | 0.23 |
| Fallopian | 15 (14.9%) | 12 (17.4%) | 3 (9.4%) | |
| Peritoneum | 8 (7.9%) | 7 (10.1%) | 1 (3.1%) | |
| Pathologic Stage | | | | |
| III | 86 (85.1%) | 59 (85.5%) | 27 (84.4%) | 1.00 |
| IV | 15 (15.6%) | 10 (14.5%) | 5 (15.6%) | |
| Grade | | | | |
| G2/3 | 101 (100%) | 69 (100%) | 32 (100%) | -- |
| Surgical outcome | | | | |
| 0 | 45 (44.6%) | 33 (47.8%) | 12 (37.5%) | 0.04 |
| 1-10mm | 40 (39.6%) | 22 (31.9%) | 18 (56.3%) | |
| >10mm | 16 (15.8%) | 14 (20.3%) | 2 (6.3%) | |

* p-values for Diagnosis, Grade, OR Tumor Index by Pearson Chi-Square, Pathologic Stage, Surgical outcome by Fisher's Exact, age by ANOVA (all p-values are double-sided)

**Table 2**

TCGA Patients Baseline Demographics

| **Variables** | **All** | **BRCA (-)** | ***BRCA1/2* (+)** | ***P*-value*** |
|---|---|---|---|---|
| Whole Cohort | 266 | 229 | 37 | |
| Age (6 missing) | | | | |
| Median (mean) | 60.9 (61.0) | 61.4 (61.9) | 53.7 (55.7%) | <0.01 |
| Range | 35.0 - 84.9 | 35.0 - 84.7 | 38.9 - 76.0 | |
| Stage | | | | |
| III | 227 (85.3%) | 194 (84.9%) | 33 (89.2%) | 0.62 |
| IV | 39 (14.7%) | 35 (15.3%) | 4 (10.8%) | |
| Grade (4 missing) | | | | |
| G2/3 | 262 (100%) | 225 (100%) | 37 (100%) | -- |
| Surgical outcome | | | | |
| 1-10mm | 143 (53.8%) | 124 (54.1%) | 19 (51.4%) | |
| >10mm | 84 (31.6%) | 75 (32.8%) | 9 (24.3%) | |

* p-value for Stage, Grade by Fisher's Exact test, Surgical outcome by Pearson Chi-Square (all p-values two-sided), age by ANOVA

**Table 3**

*BRCA1/2* Subset Analysis (MSKCC and TCGA Patients Combined)

| **Variables** | **All** | **BRCA (-)** | ***BRCA1* (+)** | ***BRCA2* (+)** | ***P*-value** |
|---|---|---|---|---|---|
| Whole Cohort | 367 | 298 | 38 | 31 | |
| Surgical outcome | | | | | |
| 0-10mm | 267 (72.8%) | 209 (70.1%) | 33 (86.8%) | 25 (80.6%) | 0.55 |
| >10mm | 100 (27.2%) | 89 (29.9%) | 5 (13.2%) | 6 (19.4%) | |
| Surgical outcome | | | | | |
| 0mm | 84 (22.9%) | 63 (21.1%) | 12 (31.6%) | 9 (29.0%) | 0.15 |
| 1-10mm | 183 (49.9%) | 146 (49.0%) | 21 (55.3%) | 16 (51.6%) | |
| >10mm | 100 (27.2%) | 89 (29.9%) | 5 (13.2%) | 6 (19.4%) | |

*p-value's obtained by two-sided Pearson Chi-Square Test

**Table 4**

Surgical outcome Univariate Analysis (MSKCC and TCGA Patients Combined)*

| Variables | No. of Patients | Odds Ratio | 95% Confidence Interval | Log-Rank *P* |
|---|---|---|---|---|
| Age (10-years) | 361 | 1.33 | 1.07 - 1.65 | 0.01 |
| Stage | | | | |
| III | 309 | 0.81 | 0.43 - 1.54 | 0.53 |
| IV | 52 | Ref. | | |
| Patient Cohort | | | | |
| MSKCC | 101 | 0.41 | 0.23 - 0.74 | <0.01 |
| TCGA | 260 | Ref. | | |
| BRCA Status | | | | |
| BRCA (+) | 67 | 0.47 | 0.23 - 0.94 | 0.03 |
| BRCA (-) | 294 | Ref. | | |

## Table 5

Surgical outcome Multivariate Analysis (MSKCC and TCGA Patients Combined)*

| Variables | No. of Patients | Odds Ratio | 95% Confidence Interval | *P*-value |
|---|---|---|---|---|
| Age (10 years) | 361 | 1.25 | 1.01 - 1.56 | 0.05 |
| Cohort | | | | |
| MSKCC | 101 | 0.47 | 0.25 - 0.85 | 0.01 |
| TCGA | 260 | Ref. | | |
| BRCA | | | | |
| BRCA (+) | 67 | 0.63 | 0.31 -1.29 | 0.21 |
| BRCA (-) | 294 | Ref. | | |

*All estimates reflect binary logistic model predicting for optimal versus suboptimal debulking (optimal include 0mm and 0-10mm), reference outcome sub-optimal debulking