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Altered Significance of D'Amico Risk Classification in Prostate Cancer Patients linked to a Familial Breast Cancer (kConFab) cohort.

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Abstract:

Objectives:

- To ascertain whether D'Amico risk classification is an accurate discriminator of prostate cancer mortality risk in *BRCA2* pathogenic mutation carriers and non-carriers from a familial breast cancer cohort.

Patients and methods:

- From family cancer pedigrees of patients evaluated through a familial breast cancer cohort all related men with a diagnosis of prostate cancer were identified.
- Genotyping of each patient or of the dominant familial *BRCA2* mutation was undertaken in each instance.
- Prostate cancers were analysed by *BRCA2* carrier vs non carrier status for their clinical progression and survival according to their D'Amico risk groups.

Results:

- For patients who were *BRCA2* mutation positive, there was no significant difference in disease specific disease specific survival between those patients who were graded as having D'Amico high- or intermediate-risk disease.
- For patients who were *BRCA2* mutation negative, but were identified via a family cancer pedigree, no statistically significant difference in disease specific survival was noted between D'Amico high-risk and intermediate-risk prostate cancer.
- Patients with D'Amico high-risk disease who were *BRCA2* mutation carriers had substantially increased disease specific mortality in comparison to high risk non-carriers (HR 2.94, p= 0.0038).

Conclusions:

- D'Amico risk classification has limitations in predicting variations in prostate cancer-specific mortality for this group of patients.

Introduction:

BRCA2 is a multisite tumour suppression gene, in which mutations are associated with an increased risk of breast and ovarian cancers[1-2]. This gene has been shown to be associated with an increased risk of, and a higher disease-specific mortality rate for prostate cancer in men who are carriers of a pathogenic *BRCA2* mutation[3-6]. This is presumably related at least in part to a

previously documented increased risk of high-grade disease where prostate cancer has been detected[7-10].

Decisions regarding optimal management of localized prostate cancer are currently based on the assessment of an individual's treatment preferences, the tumour stage/Gleason score and consequent risk of disease progression, and expected patient longevity[11]. D'Amico risk classification has been used clinically to predict risks of biochemical recurrence after treatment with curative intent, as well as likelihood of progression to metastatic disease and overall survival[12]. This classification stratifies patients into low-, intermediate- and high-risk groups for tumour recurrence and prostate cancer-specific mortality based on PSA, Gleason score and clinical/pathologic staging[13].

Despite being validated in large patient cohorts, the suitability of D'Amico risk classification has not been analyzed specifically for patients identified via a familial cancer clinic or for patients who are *BRCA2* mutation carriers. We sought to address these issues by reference to patients from families with a known *BRCA* mutation status evaluated via a familial cancer clinic.

Patients and Methods:

Patient Population

The Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (KConFab – www.kconfab.org) began enrolling families with a strong history of breast or ovarian cancers in 1997 in Australia and New Zealand through Familial Cancer Clinics[14]. Within this multigenerational cohort, 147 men were identified with histologically confirmed prostate cancer and a verified *BRCA* mutation status, who had all come from families with a strong familial history of breast cancer. Thirty-nine men (26.5%) were *BRCA2* mutation carriers, 11 (7.5%) were *BRCA1* mutation carriers, and 97 (66%) were non-carriers. The non-carriers were defined as those who either tested negative for their family specific *BRCA1* or *BRCA2* mutation, or where no pathogenic germ-line mutation had been identified in the youngest cancer affected family member (*BRCAX*). Due to the small number of *BRCA1* carriers (n=11) this group was excluded, leaving 136 men who were subsequently divided for further analysis according to the D'Amico risk stratification of their prostate cancer.

Due to the highly selected nature of this familial cancer based patient cohort, the D'Amico low-risk prostate cancer group (11 patients) was thought to have too few participants for valid analysis. Although this small number of patients with low-risk disease is a valid observation in itself, our subsequent analysis focused on the intermediate- and high-risk groups where statistically significant variations were potentially identifiable. These prostate cancer

patients were divided into four groups for comparison: *BRCA2* mutation carriers in the intermediate-risk group (carrier intermediate) and high-risk group (carrier high); and non-carriers of a *BRCA2* mutation in the intermediate-risk group (non-carrier intermediate) and high-risk group (non-carrier high).

Clinical details

All patients had prostate adenocarcinoma diagnosed at Trans Rectal Ultrasound guided Biopsy or Transurethral Resection of the Prostate. The date of the original histopathology report was used to record the date of cancer diagnosis and was the basis for D'Amico risk classification. All patients had undergone radiologic staging, and those with no evidence of metastases had been treated with either radical retropubic prostatectomy or external beam radiation therapy. Patients with metastatic disease were managed with androgen deprivation therapy using LHRH agonists as first line therapy. Evaluable data including baseline biochemical results and radiologic staging to detect metastatic disease, plus longer term follow up was assessed by analysis using the kConFab database.

Statistical Analyses

To study the impact of a *BRCA2* mutation, comparisons were carried out between carriers and non-carriers in the same risk group (e.g. carrier intermediate vs. non-carrier intermediate). In order to examine the validity of D'Amico risk classification, comparisons were done between different risk groups with the same mutation status (e.g. carrier intermediate vs. carrier high) using Cox Proportional Hazard.

Kaplan-Meier curves were used to analyze prostate cancer-specific survival stratified by *BRCA2* status, including patients who had and had not progressed to biochemical recurrence (BCR). For patients with D'Amico high-risk disease at diagnosis, long-term follow up was available for 30/31 men who were *BRCA2* mutation carriers and 54/59 men who were non-carriers of a mutation. For patients in the cohort with D'Amico intermediate-risk disease, long term follow up was available for 27/31 men who were non-carriers and 4/5 men who were carriers of a *BRCA2* mutation.

Results:

Based on D'Amico risk classification of prostate cancer, 11 (7%) patients had low-risk disease, 36 (26%) were in the intermediate-risk group and the majority (n=90, 67%) had high-risk disease (Figure 1). This is in sharp contrast to the distribution of participants with prostate cancer in the general population. The CaPSURE study of a broadly based US population showed that contemporaneously among patients with prostate cancer, only 13% had high-risk disease, 47% were in the low-risk group, and 40% in the intermediate-risk group[15].

There were no significant differences in the age or serum PSA level at diagnosis among all four groups (Table 1). However it appears that both carriers and non-carriers in this familial cancer based cohort had a younger median age at diagnosis (65-71 years) than the general population. A contemporary study on 8,887 men from a Swedish population-based registry showed their median age at diagnosis was 75 years with only 12% 65-years or younger[16], in contrast to the median age of 66-years in this cohort.

When patients from this familial cancer cohort with the same *BRCA* carrier status were compared with respect to D'Amico risk grading, the D'Amico status was not found to be strongly predictive of the variance in outcomes that

has been demonstrated in more widely sourced prostate cancer patient cohorts. For patients who were carriers of the *BRCA2* mutation, statistical significance for difference in cancer-specific survival was approached but not reached, between patients with D'Amico high-risk and intermediate-risk disease (p = 0.06, Figure 2a). Similarly, for patients in this series who were not carriers of a *BRCA2* mutation but, by definition, whose prostate cancers were linked via a family cancer pedigree to our familial–inheritance based breast cancer cohort, no statistically significant difference in disease specific survival was noted between patients with D'Amico high-risk and D'Amico intermediate-risk prostate cancer (p = 0.22, Figure 2b).

In terms of *BRCA2* carrier status, a clearly poorer outcome was noted for patients with D'Amico high-risk disease who were *BRCA2* carriers compared to those who were non-carriers of this mutation (Figure 3). Patients with D'Amico high-risk disease who were *BRCA2* mutation carriers had substantially increased disease specific mortality by comparison to non-carriers (HR 2.94, p= 0.0038). Although D'Amico high-risk disease did predict for a poor outcome in terms of cancer-specific survival in both groups, the impact of *BRCA2* status is significant and was shown to be an independent risk factor for poorer survival. The projected 15-year survival was found to be 47% for non-carriers and 0% for carriers.

In contrast, no significant difference in survival was noted in patients with D'Amico intermediate-risk disease between patients who were *BRCA2* carriers and those who were non-carriers of this mutation (p = 0.35, Figure 3b). The projected 15-year survival was 46% for the non-carriers and 33% for the carriers. These survival rates however, are much lower than those reported for intermediate-risk disease in the general population, which range from 54% to 89%[15].

Overall the D'Amico intermediate-risk group did not have significant difference in the 15-year survival compared with the high-risk group for both carriers and non-carriers. However, for patients who had died of prostate cancer, those with intermediate-risk disease had survived longer than those high-risk patients (mean time to death: carriers 9.0 vs. 4.0 years, p=0.065; non-carriers: 10 vs. 4 years, p=0.001).

As detailed in the patients and methods section the small number of patients with low risk disease precluded valid statistical analysis of this cohort, but the results of this group are presented for completion. No patient in this group was managed by active surveillance. Two patients were treated by radical prostatectomy and both were alive at 8 years post surgery, with one having progressed to metastatic disease and requiring androgen deprivation therapy. Nine patients were treated by external beam radiation and androgen deprivation

therapy, and mean post treatment follow up was to 7.4 years post diagnosis. In that time two of these patients had deceased from prostate cancer.

Discussion:

This kConFab derived cohort has a much higher proportion of patients with high-risk disease in both *BRCA2* carriers and non-carriers compared with the general population[15], and their age at diagnosis is younger than that reported in large prostate cancer cohorts[16]. This observation is consistent with other series, with a greater than normal prevalence of patients who are carriers of a *BRCA2* pathogenic mutation. The relatively high prostate cancer-specific mortality noted in this series, even for patients who are non-carriers of the mutation, suggests that a family history of a pathogenic mutation in *BRCA2* is significant in terms of the potential to fail to achieve a curative outcome from the treatment of apparent organ confined disease. This is a significant point when considering the age at which prostate cancer screening should commence in this group of men.

The impact of a *BRCA2* mutation on progression and survival was clearly demonstrated in patients with high-risk disease. *BRCA2* mutation carriers had significantly higher mortality risk than non-carriers (HR 2.94). A strong case may be made for treatment with curative intent at the earliest possible time in such cases where apparent organ confined disease has been identified.

Using D'Amico risk classification, the differences in disease specific survival for both carriers and non-carriers between the intermediate- and high-risk groups were not as substantial as that which has been observed in the general population. This reflects the more aggressive phenotype of the prostate cancer displayed by men in this familial cancer cohort and emphasizes the significance of a *BRCA2* mutation and family cancer history in managing patients with prostate cancer, even for those patients where prostate biopsy has identified intermediate-risk disease. Alternative cancer detection and intervention strategies should be considered for this unique group.

The absence of any statistically significant difference in survival between *BRCA2* mutation positive patients with D'Amico high- and intermediate-risk disease suggests that consideration should be given to avoiding active surveillance treatment protocols in this patient group, even though the failure rate for active surveillance in selected instances of D'Amico intermediate-risk disease has previously been suggested to be low. In addition, the poorer than usual survival outcomes for both carriers and non-carriers with D'Amico intermediate-risk disease suggests that this premise may potentially be applied to all patients with intermediate-risk disease where there is a strong family history of breast cancer. If active surveillance strategies are to be implemented in such patients, then a low threshold should exist for additional intervention with repeat biopsies or imaging, given that prostate cancer-specific mortality is

higher in these patient sub-groups than in the general population of men with prostate cancer.

Although the above conclusions of the study appear statistically justifiable one limitation of the work which is that within the study there is a relatively limited number of men with prostate cancer. Additionally prostate cancer was likely not detected via systematic screening (the age of diagnosis is lower compared to a swedish population but higher than screened populations such as those in the US) but rather by case selection based at least in part by a knowledge of the family histories of BRCA related cancer. We plan to commence a prospective matched cohort study which will take some years to mature but will help further develop hypotheses regarding men where the BRCA2 mutation is present.

Although D'Amico risk classification has an established role in the assessment of disease progression risk and prostate cancer-specific mortality, there may be more limited utility of this grading system where patients have tested positive for a pathogenic *BRCA2* genetic mutation or have a strong family history of breast cancer.

Conflicts of Interest: None disclosed.

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Legend to Figures:

Figure 1: Distribution of *BRCA2* carriers and non-carriers according to D'Amico risk classification.

Figure 2a: Disease specific survial for *BRCA2* carriers with intermediate- and high-risk disease. No statistically signficant survival difference was found (p=0.06).

Figure 2b: Disease specific survial for *BRCA2* non-carriers with intermediate- and high-risk disease. No statistically signficant survival difference was found (p=0.22).

Figure 3a: Disease specific survival for patients with high-risk disease *BRCA2* carriers vs. non-carriers (p<0.005).

Figure 3b: Disease specific survival for patients with intermediate-risk disease *BRCA2* carriers vs non-carriers (p=0.35).

Table 1: Mean and Median age and PSA at diagnosis

Groups (n)	Median Age (range)	Mean Age ±SD	Median PSA (range)	Mean PSA ±SD
Carrier Intermediate (5)	71 (55-77)	68 ±9	8.9 (4.4-14.9)	9.28 ± 4.5
Non-carrier Intermediate (31)	67 (33-78)	66 ±9	8.2 (0.72 – 19.2)	8.6 ± 5.1
Carrier High (31)	65 (43-84)	66 ±9	20.95 (0.4 – 3750)	235.9 ± 783
Non-carrier High (59)	66 (45-87)	66 ±10	10.0 (2-195)	22.9 ± 35.3

Table 2: Clinico-pathological Data at diagnosis

Groups (n)	Tumour Stage at Diagnosis	Gleason score	Mode of treatment
Carrier Intermediate (5)	T1b=2 T1c=2 T2c=1	3+4=7 (3) 4+3=7 (2)	Radical Prostatectomy =1 Radical Prostatectomy & Radiation =2 Radiation & AD =2
Non-carrier Intermediate (31)	T1b= 3 T1c= 12 T2c= 2 T3a= 7 T3b= 6 T4N1M1=1	3+4=7 (13) 4+3=7 (18)	Radical Prostatectomy =7 Radical Prostatectomy & Radiation = 3 Radiation & AD = 14 Radical Prostatectomy & Radiation & AD = 5 Androgen Deprivation = 1 Uncertain = 1
Carrier High (31)	T1bN0M0= 4 T1cN0M0= 9 T1cN0M1= 1 T2cN0M0= 1 T3aN0M0= 8 T3bN0M0= 3 T3bN1M0= 1 T4N1M1= 2 Uncertain = 2	3+4=7 (2) 4+3=7 (3) 4+4= 8 (13) 4+5= 9 (9) 5+4 = 9 (2) 5+5 = 10 (2)	Radical Prostatectomy =3 Radical Prostatectomy & Radiation = 1 Radical Prostatectomy & AD = 5 Radiation only = 3 Radiation & AD = 12 Radical Prostatectomy & Radiation & AD = 6 Androgen Deprivation = 1
Non-carrier High (59)	T1bN0M0= 6 T1cN0M0=28 T2cN0M0=11	3+4=7 (4) 4+3=7 (4) 4+4= 8 (37)	Radical Prostatectomy =3 Radical Prostatectomy & Radiation = 1

	T3aN0M0=7 T3bN0M0= 5 T4N0M1= 2	4+5= 9 (11) 5+4 = 9 (3)	Radical Prostatectomy & AD = 5 Radiation & AD = 32 Radiation only = 1 Radical Prostatectomy & Radiation & AD = 6 Androgen Deprivation = 1

Figure 1

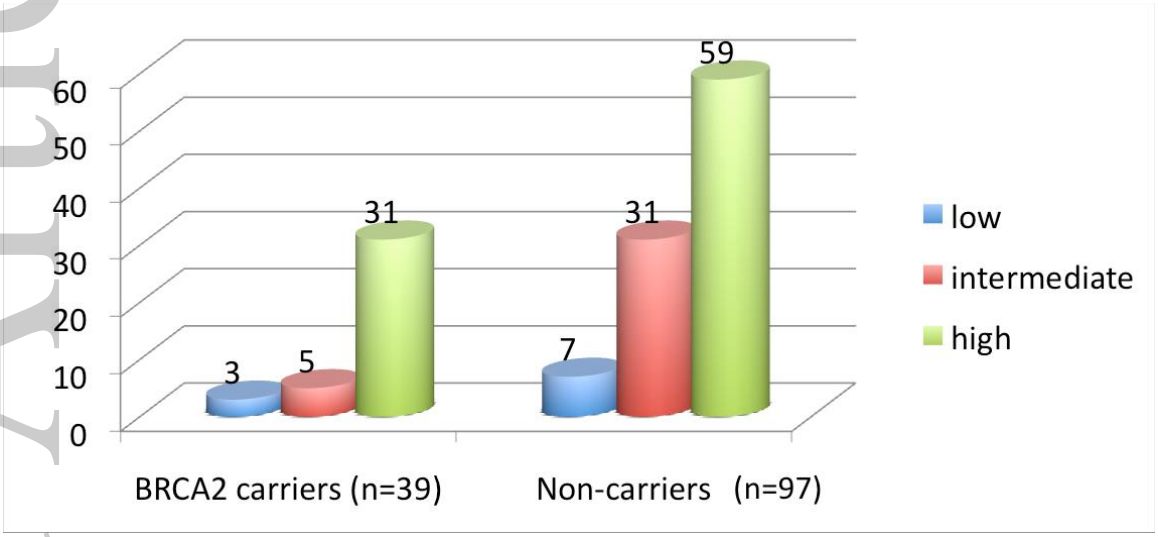

Figure 2a

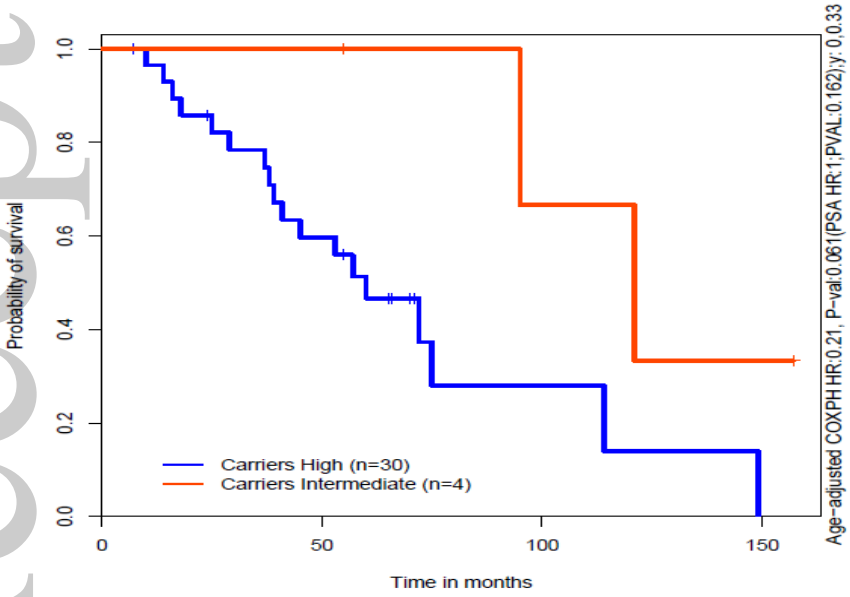

Figure 2b

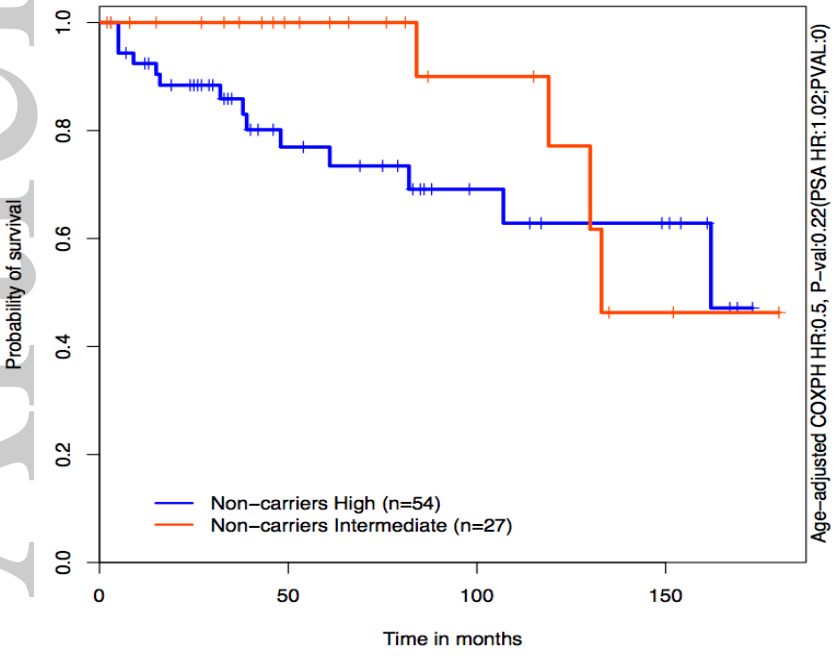

Figure 3a

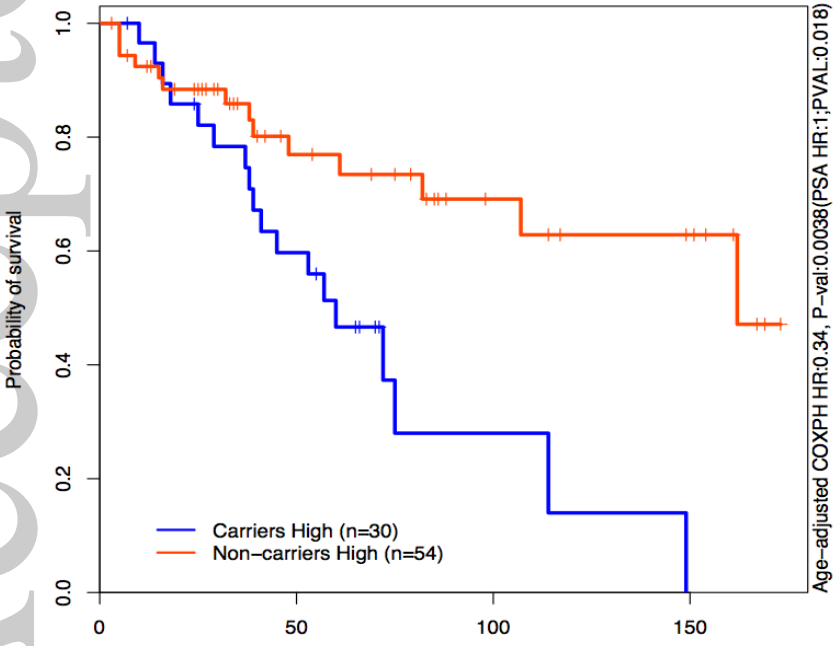

Figure 3b