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DNA-Repair Gene Mutations in Metastatic Prostate Cancer

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TO THE EDITOR:

The study by Pritchard et al. (Aug. 4 issue)¹ has major implications for translational science, and it provides support for germ-line genetic testing to determine the risk of aggressive prostate cancer. In our sequencing analysis involving a large population of men who died of prostate cancer (unpublished data), we observed similar findings regarding germline mutations, with one interesting exception: *CHEK2*.

Pritchard et al. found that germline mutations of *CHEK2* (mostly founder mutations)^{2,3} were significantly more common in men in their study who had metastatic prostate cancer than in men with localized prostate cancer in the Cancer Genome Atlas cohort (Table 2 of the article). Although this finding is intriguing, it may be influenced by the difference in the genetic makeup of the comparison groups (i.e., population stratification), particularly when founder mutations were present.

After we removed data on known founder mutations and limited the population to whites, our reanalysis of the data by Pritchard et al. revealed a smaller, nonsignificant difference between the two groups (Table 1). Furthermore, the analysis involving our study cohort showed no significant difference between white men who died of prostate cancer and those who received a clinical diagnosis of localized prostate cancer with respect to the rate of carriers of the *CHEK2* mutation. Additional studies are warranted to further evaluate this potentially important finding.

References

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No potential conflict of interest relevant to this letter was reported.

Table 1.

Carriers of *CHEK2* Germline Mutations among Men with Prostate Cancer.

Study	Race	Mutation Carriers		P Value*
		Men with Metastatic Prostate Cancer	Men with Localized Prostate Cancer	
no./total no. (%)				
Pritchard et al. ^{1,7}				
Original results	Mixed	10/692 (1.45)	2/499 (0.40)	<0.001
Excluding founder mutations [‡]	Mixed	4/692 (0.58)	0/499	0.14
Excluding founder mutations in whites only	White	1/576 (0.17) ^{\$}	0/406	1.00
Cohort from Johns Hopkins Hospital and NorthShore University HealthSystem ^{8//}				
Original results	White	5/261 (1.924)	6/352 (1.70)	1.00
Excluding founder mutations ^{8//}	White	2/261 (0.77)	2/352 (0.57)	1.00

* All P values were calculated with the use of Fisher's exact test.

[‡] Data on men with localized prostate cancer were obtained from the Cancer Genome Atlas database. Founder mutations were 1100delC, 1283C→T, and 470T→C.

[§] Four men who carried 1100delC founder mutations and two who carried 1283C→T founder mutations in the study by Pritchard et al. were excluded. Two men who carried the 1100delC founder mutation in the Cancer Genome Atlas cohort were excluded.

^{||} One Asian carrier and two carriers for whom information on race was unknown were excluded.

[¶] The study population from Johns Hopkins Hospital and NorthShore University HealthSystem included men who died of metastatic prostate cancer and those who received a clinical diagnosis of localized prostate cancer.

^{|||} Two carriers of the 1100delC founder mutation and one carrier of the 470T→C founder mutation were excluded from the group of men who died of prostate cancer, and two carriers of the 1283C→T founder mutation, one carrier of the 1100delC founder mutation, and one carrier of 470T→C founder mutation were excluded from the group of men with indolent prostate cancer.