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ORIGINAL PAPER

Polymorphisms of the *AURKA* (*STK15/Aurora kinase*) gene and breast cancer risk (United States)

David G. Cox · Susan E. Hankinson · David J. Hunter

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Abstract AURKA is an important protein in the regulation of G_2 to M transition during mitosis. Due to this regulatory function, it has been hypothesized to be a potential cancer susceptibility gene. Two non-synonymous polymorphisms (F31I and V57I) have been associated with breast cancer risk in prior studies. We sought to confirm these findings in a large case control study nested within a prospective cohort, the Nurses' Health Study. Post-menopausal women who were homozygous for the 31I and 57V alleles had an increased risk of invasive breast cancer (OR 1.63, 95% CI 1.08–2.45). We also performed a meta-analysis to summarize the findings of this and prior studies of association between the F31I polymorphism and breast cancer risk (Summary OR 1.29, 95% CI 1.08–1.53, *p*-heterogeneity = 0.29). These results confirm prior findings that *AURKA* represents a low penetrance breast cancer susceptibility gene.

Keywords Aurora kinase · AURKA · Breast cancer · SNP

D. G. Cox (✉) · S. E. Hankinson · D. J. Hunter
Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave., MA 02115, Boston, USA
Fax: +1-(617)-432-1722
e-mail: dcox@hsph.harvard.edu

S. E. Hankinson · D. J. Hunter
Department of Medicine, Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

D. G. Cox · D. J. Hunter
Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, USA

Introduction

AURKA (*STK15, Aurora kinase*) is involved in cell cycle regulation, in particular the passage from G_2 to M, through the formation of mitotic spindle formation [1]. While this gene is found to be amplified in many tumor types, including breast cancer [2], the loss of over expression of *AURKA* has been correlated with the transition of *in situ* to invasive ductal carcinoma [3].

Ewart-Toland *et al*. [4] found that the polymorphic Ile allele of F31I was more effective at transforming rat cells to a more malignant phenotype. This and other polymorphisms have been associated with breast cancer risk in four retrospective case-control studies (Table 1). Sun *et al*. found a significant increase in risk (OR 1.76, 95% CI 1.16–2.66) associated with the homozygous state of the Ile allele at the F31I (rs2273535) polymorphism of *AURKA*, while Dai *et al*. did not (OR 1.2, 95% CI 0.9–1.6), in hospital-based [5] and population-based [6] case-control studies of Han Chinese women. Lo *et al*. also did not observe a statistically significant (p=0.32 of association under an additive model) association between this polymorphism and breast cancer risk in a hospital based case-control study in Taiwan [7], however they did observe association between haplotypes of *AURKA* and breast cancer. It is interesting to note that the prevalence of the homozygous state of the Ile allele in Asian populations (∼45%) is drastically different that that of Caucasians (∼4%). Egan *et al*. described an increase in risk associated with a compound genotype of two non-synonymous polymorphisms, F31I and V57I (rs1047972), with individuals homozygous for the 31I and 57V alleles having a nearly 2-fold increase in risk of postmenopausal invasive breast cancer [8]. We studied these two poly-

Table 1 Prior reports of association between the F31I Polymorphism and breast cancer risk

Study	Cases (%)	Controls (%)	OR (95% CI)
Egan *et al.* [8][a]			
F31F	559 (59.5)	516 (62.2)	1.00 (Ref.)
F31I	331 (35.2)	283 (34.1)	1.10 (0.90–1.34)
I31I	50 (5.3)	31 (3.7)	1.54 (0.96–2.47)
Dai *et al.* [6][b]			
F31F	121 (11.0)	149 (12.6)	1.00 (Ref)
F31I	491 (44.6)	503 (42.4)	1.3 (1.0–1.7)
I31I	490 (44.5)	534 (45.0)	1.2 (0.9–1.6)
Lo *et al*. [7][c]			
F31F	71 (10.0)	196 (10.0)	1.00 (Ref.)
F31I	288 (40.7)	887 (45.0)	0.90 (0.66–1.21)
I31I	348 (49.3)	886 (45.0)	1.08 (0.81–1.46)
Sun *et al*. [5][d]			
F31F	50 (9.6)	66 (12.7)	1.00 (Ref.)
F31I	214 (41.1)	262 (50.4)	1.08 (0.72–1.62)
I31I	256 (49.3)	192 (36.9)	1.76 (1.17–2.65)

[a] Table 2, unconditional logistic regression adjusted for age, state of residence, parity, age at first birth, menopausal status, BMI, HRT use, and family history of breast cancer

[b] Table 2, logistic regression adjusted for age, personal history of fibroadenoma, WHR, age at first birth, age at menarche, physical activity, and menopausal status

[c] Crude OR as calculated from Table 1

[d] Crude OR as calculated from Table 2

morphisms in a case-control study nested within the prospective Nurses' Health Study.

Materials and methods

Genotyping assays for the *AURKA* polymorphisms (F31I, rs2273535; and V57I, rs1047972) were performed by the 5′ nuclease assay (TaqMan) on the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). TaqMan primers, probes, and conditions for genotyping assays are available on request from the authors. Our study included a total of 1259 incident breast cancer cases (1021 invasive, 208 *in situ* and 30 unknown or undetermined histology) diagnosed after blood draw up to June 1, 2000, and 1742 matched controls, drawn from 32,826 women who gave a blood sample in 1989–90. Controls were randomly selected participants who were free of diagnosed cancer (except non-melanoma skin cancer), and matched to cases based on age, menopausal status, recent post-menopausal hormone use, and time, day, and month of blood collection. Greater than 95% of the samples were successfully genotyped on the first attempt, with samples that failed genotyping being removed from further analyses.

We used SAS v8.2 (SAS Institute, Cary, NC) for most statistical analyses. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using both conditional and unconditional logistic regression, controlling for matching factors, age at menopause, age at menarche, age at first birth and parity, history of benign breast disease, and family history of breast cancer using PROC PHREG (conditional regression) and PROC LOGISTIC (unconditional regression). We tested for departures from Hardy-Weinberg equilibrium using PROC ALLELE. Interactions were tested by likelihood ratio tests comparing the model with main effects for each variable of interest to the model with the two variables cross-tabulated. Meta-analyses were conducted using the rmeta package in R 1.7.1. All *p*-values reported are two sided.

Results and discussion

Our results were similar to those observed by Egan *et al*. [8]. Meta-analyses of the prior studies (shown in Table 1) and our study show a significant increase in breast cancer risk for women homozygous for the I allele of F31I (Summary OR 1.28, 95% CI 1.08–1.53). The test of heterogeneity between studies was not significant ($p = 0.29$).

Both polymorphisms studied were in Hardy-Weinberg equilibrium in controls ($p>0.41$). There were no significant differences in risk estimates generated by conditional and unconditional models, and Table 2 reports those from the multivariate unconditional regressions. We observed a borderline significant association between homozygosity of the 31I allele and overall breast cancer risk (OR 1.40, 95% CI 0.97–2.02, Table 2). No statistically significant association was observed with the V57I polymorphism. When restricting our analyses to post-menopausal women, those homozygous for the 31I allele were at 57% increased risk of invasive breast cancer (OR 1.57, 95% CI 1.05–2.33, Table 2). Our results in combining the two genotypes are similar to those seen by examining the V31I allele alone. In analyses restricted to post-menopausal women, we found that women homozygous for both the 31I and 57V were at 63% increased risk of invasive breast cancer (OR 1.63, 95% CI 1.08–2.45, Table 2). We observed, a higher risk of invasive breast cancer in lean post-menopausal women homozygous for 31I (BMI < median of 25 kg/m^2, OR 1.90; 95% CI 1.11–3.25), as opposed to heavier post-menopausal women (BMI ≥ median of 25 Kg/m^2, OR 1.06; 95% CI 0.64–1.76).

Egan *et al*. had observed that heavier women were at increased risk with the 31I homozygous genotype when contrasted with leaner women. However, since neither the *p*-value for the interaction in our study (p=0.27) or theirs (p=0.99) was statistically significant between BMI and

Table 2 Association between *AURKA* polymorphism and breast cancer risk in the Nurses' Health Study

	Overall			Pre-menopausal			Post-menopausal			Invasive post-menopausal		
	Cases (%)	Controls (%)	OR (95% CI)[a]	Cases (%)	Controls (%)	OR (95% CI)[a]	Cases (%)	Controls (%)	OR (95% CI)[a]	Cases (%)	Controls (%)	OR (95% CI)[a]
F31I												
FF	774 (62.4)	1075 (62.8)	1.00 (Ref.)	59 (57.3)	68 (60.7)	1.00 (Ref.)	658 (61.7)	947 (62.5)	1.00 (Ref.)	554 (61.0)	947 (62.5)	1.00 (Ref.)
FI	401 (32.3)	571 (33.4)	1.00 (0.85–1.17)	39 (37.9)	40 (35.7)	1.26 (0.69–2.29)	350 (32.8)	508 (33.6)	1.00 (0.84–1.19)	301 (33.1)	508 (33.6)	1.02 (0.85–1.23)
II	66 (5.3)	65 (3.8)	1.43 (0.99–2.06)	5 (4.9)	4 (3.6)	1.22 (0.30–4.97)	59 (5.5)	59 (3.9)	1.46 (0.99–2.15)	53 (5.8)	59 (3.9)	1.59 (1.07–2.37)
V57I												
VV	870 (70.2)	1215 (70.5)	1.00 (Ref.)	76 (71.0)	79 (69.3)	1.00 (Ref.)	745 (70.3)	1084 (71.2)	1.00 (Ref.)	628 (69.4)	1084 (71.2)	1.00 (Ref.)
VI	342 (27.6)	462 (26.8)	1.04 (0.88–1.24)	28 (26.2)	27 (23.7)	1.23 (0.64–2.36)	294 (27.7)	400 (26.3)	1.08 (0.90–1.30)	259 (28.6)	400 (26.3)	1.12 (0.93–1.36)
II	28 (2.3)	47 (2.7)	0.80 (0.49–1.30)	3 (2.8)	8 (7.0)	0.38 (0.09–1.55)	21 (2.0)	39 (2.6)	0.76 (0.44–1.32)	18 (2.0)	39 (2.6)	0.78 (0.44–1.40)
Combined												
FF_VV	476 (39.0)	684 (40.4)	1.00 (Ref.)	34 (33.3)	40 (35.7)	1.00 (Ref.)	406 (38.7)	611 (40.8)	1.00 (Ref.)	338 (37.7)	611 (40.8)	1.00 (Ref.)
FI_VV	316 (25.9)	443 (26.2)	1.05 (0.87–1.27)	34 (33.3)	33 (29.5)	1.35 (0.67–2.71)	273 (26.0)	395 (26.4)	1.06 (0.87–1.30)	231 (25.8)	395 (26.4)	1.07 (0.87–1.33)
II_VV	65 (5.3)	64 (3.8)	1.48 (1.01–2.15)	5 (4.9)	4 (3.6)	1.27 (0.30–5.33)	58 (5.5)	58 (3.9)	1.53 (1.03–2.28)	52 (5.8)	58 (3.9)	1.68 (1.11–2.53)
FF_VI	254 (20.8)	331 (19.5)	1.12 (0.91–1.37)	21 (20.6)	20 (17.9)	1.37 (0.62–3.07)	216 (20.6)	284 (19.0)	1.17 (0.93–1.46)	188 (21.0)	284 (19.0)	1.21 (0.96–1.53)
FI_VI	82 (6.7)	125 (7.4)	0.98 (0.72–1.33)	5 (4.9)	7 (6.3)	1.14 (0.31–4.20)	74 (7.1)	110 (7.3)	1.03 (0.74–1.42)	68 (7.6)	110 (7.3)	1.13 (0.80–1.58)
FF_II	28 (2.3)	47 (2.8)	0.82 (0.50–1.35)	3 (2.9)	8 (7.1)	0.44 (0.10–1.90)	21 (2.0)	39 (2.6)	0.80 (0.46–1.39)	18 (2.0)	39 (2.6)	0.83 (0.46–1.49)

[a] Unconditional logistic regression, controlled for matching factors, age at menopause, age at menarche, family history of breast cancer, personal history of benign breast disease, and post-menopausal hormone replacement therapy at diagnosis. Number of cases and controls in the pre- and post-menopausal analyses do not add up to the overall numbers due to subjects with uncertain menopausal status

AURKA genotypes on breast cancer risk, these differences are most likely due to chance. In pre-menopausal women, Egan *et al*. observed a non-significant inverse association among women homozygous for the I allele at V57I (OR 0.38, 95% CI 0.14–1.07) which is very similar to our study (OR 0.35 95% CI 0.09–1.44). While neither study has large numbers of pre-menopausal women, the similarity between the two findings warrants examination in studies with larger numbers of pre-menopausal women. We observed no difference in the distribution of BMI or duration of menstruation (menarche to first birth or menopause in nulliparous women) between genotypes among cases or controls (data not shown). No differences in risk were observed upon stratification by history of benign breast disease, first degree family history of breast cancer, or estrogen/progesterone receptor status of tumors in the cases.

In conclusion, these polymorphisms in the *AURKA* gene appear to be associated with an increase in breast cancer risk, which is similar in both Caucasian and Asian populations. This increase in risk is independent of established hormone related risk factors for breast cancer.

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