

THE LANCET

Supplementary webappendix

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Supplement to: Travis RC, Reeves GK, Green J, et al. Gene–environment interactions in 7610 women with breast cancer: prospective evidence from the Million Women Study. *Lancet* 2010; published online June 2, 2010. DOI:10.1016/S0140-6736(10)60636-8

Webtable 1: Per allele relative risk (95% CI) of breast cancer by the 8 SNPs most strongly related to breast cancer risk and by the continuous environmental factors and by HRT use subdivided into 3 groups.

	<i>FGFR2</i> - rs2981582(A)	<i>TNRC9</i> - rs3803662(A)	<i>2q35</i> - rs13387042(A)	<i>MAP3K1</i> - rs889312(C)	<i>8q24</i> - rs13281615(G)	<i>2p</i> - rs4666451(G)	<i>5p12</i> - rs981782(A)	<i>CASP8</i> - rs1045485(G)
All women	1.22 (1.17-1.28)	1.18 (1.13-1.24)	1.16 (1.11-1.21)	1.13 (1.08-1.19)	1.08 (1.04-1.13)	1.08 (1.03-1.13)	1.07 (1.02-1.11)	1.05 (0.99-1.12)
By age at menarche								
<13	1.18 (1.10-1.26)	1.25 (1.16-1.35)	1.22 (1.14-1.31)	1.13 (1.04-1.22)	1.09 (1.01-1.17)	1.11 (1.04-1.20)	1.07 (0.99-1.14)	1.07 (0.97-1.19)
13	1.21 (1.11-1.32)	1.14 (1.04-1.25)	1.12 (1.03-1.22)	1.18 (1.07-1.29)	1.03 (0.94-1.12)	1.08 (0.99-1.18)	1.05 (0.96-1.14)	1.04 (0.91-1.18)
14+	1.27 (1.18-1.37)	1.15 (1.06-1.25)	1.11 (1.03-1.20)	1.10 (1.01-1.19)	1.12 (1.04-1.21)	1.03 (0.96-1.11)	1.08 (1.01-1.17)	1.05 (0.94-1.18)
By parity								
≤1	1.15 (1.06-1.26)	1.31 (1.19-1.44)	1.23 (1.13-1.34)	1.11 (1.01-1.22)	1.05 (0.96-1.14)	1.08 (0.99-1.18)	1.05 (0.96-1.14)	1.01 (0.89-1.15)
2	1.27 (1.19-1.35)	1.15 (1.07-1.23)	1.11 (1.04-1.18)	1.09 (1.02-1.17)	1.09 (1.02-1.16)	1.07 (1.00-1.14)	1.04 (0.98-1.11)	1.07 (0.97-1.18)
3+	1.22 (1.13-1.33)	1.15 (1.05-1.25)	1.18 (1.09-1.28)	1.22 (1.11-1.33)	1.09 (1.01-1.19)	1.09 (1.01-1.19)	1.12 (1.04-1.22)	1.05 (0.93-1.18)
By age at first birth (parous women)								
<23	1.21 (1.12-1.32)	1.21 (1.11-1.32)	1.11 (1.03-1.21)	1.16 (1.06-1.27)	1.13 (1.04-1.23)	1.03 (0.95-1.12)	1.05 (0.96-1.13)	1.07 (0.95-1.20)
23-25	1.24 (1.13-1.35)	1.10 (1.00-1.21)	1.21 (1.11-1.32)	1.14 (1.03-1.25)	1.08 (0.99-1.18)	1.12 (1.03-1.23)	1.12 (1.03-1.22)	1.07 (0.94-1.21)
26+	1.26 (1.17-1.36)	1.20 (1.10-1.31)	1.14 (1.06-1.23)	1.11 (1.03-1.21)	1.06 (0.98-1.15)	1.08 (1.00-1.17)	1.09 (1.01-1.17)	1.03 (0.92-1.15)
By age at menopause (postmenopausal never users of HRT)								
<48	1.19 (1.01-1.40)	1.30 (1.08-1.55)	1.14 (0.96-1.34)	1.14 (0.95-1.37)	1.12 (0.95-1.32)	1.03 (0.87-1.22)	1.18 (1.00-1.38)	1.06 (0.83-1.35)
48-51	1.27 (1.10-1.45)	1.18 (1.01-1.37)	1.08 (0.94-1.23)	1.11 (0.96-1.28)	1.06 (0.93-1.22)	1.10 (0.96-1.26)	1.02 (0.89-1.17)	1.08 (0.88-1.33)
52+	1.22 (1.06-1.40)	1.00 (0.86-1.16)	1.24 (1.08-1.43)	1.15 (0.98-1.34)	1.00 (0.87-1.15)	1.05 (0.90-1.21)	1.04 (0.90-1.19)	0.96 (0.78-1.17)
By HRT use (postmenopausal women)								
never	1.22 (1.12-1.32)	1.14 (1.04-1.24)	1.14 (1.05-1.24)	1.12 (1.02-1.23)	1.05 (0.96-1.14)	1.06 (0.98-1.16)	1.06 (0.98-1.15)	1.01 (0.90-1.15)
past	1.27 (1.12-1.44)	1.28 (1.12-1.46)	1.23 (1.09-1.39)	1.16 (1.01-1.32)	1.05 (0.93-1.19)	1.16 (1.03-1.32)	1.04 (0.92-1.17)	0.89 (0.74-1.06)
current	1.18 (1.10-1.27)	1.16 (1.07-1.26)	1.13 (1.05-1.21)	1.08 (1.00-1.17)	1.12 (1.04-1.20)	1.08 (1.00-1.16)	1.09 (1.01-1.17)	1.10 (0.99-1.22)
By body mass index (kg/m²)								
<25	1.22 (1.14-1.30)	1.20 (1.12-1.29)	1.16 (1.09-1.23)	1.15 (1.07-1.23)	1.08 (1.01-1.15)	1.06 (0.99-1.13)	1.05 (0.98-1.11)	1.06 (0.96-1.16)
25-29	1.19 (1.11-1.29)	1.21 (1.12-1.32)	1.14 (1.06-1.23)	1.12 (1.04-1.22)	1.09 (1.01-1.18)	1.16 (1.07-1.25)	1.11 (1.03-1.20)	1.03 (0.93-1.15)
30+	1.33 (1.18-1.50)	1.08 (0.95-1.23)	1.23 (1.09-1.39)	1.14 (1.01-1.30)	1.11 (0.99-1.26)	0.98 (0.87-1.11)	1.03 (0.92-1.15)	1.03 (0.87-1.23)
By height (cm)								
<160	1.16 (1.06-1.26)	1.16 (1.06-1.27)	1.17 (1.07-1.27)	1.17 (1.06-1.27)	1.18 (1.08-1.28)	1.12 (1.02-1.22)	1.14 (1.05-1.24)	0.99 (0.88-1.12)
160-166	1.21 (1.13-1.30)	1.22 (1.14-1.32)	1.12 (1.05-1.20)	1.14 (1.06-1.23)	1.00 (0.94-1.07)	1.04 (0.97-1.11)	1.01 (0.95-1.08)	0.99 (0.90-1.09)
167+	1.29 (1.19-1.40)	1.16 (1.06-1.26)	1.20 (1.11-1.30)	1.12 (1.03-1.22)	1.12 (1.04-1.21)	1.13 (1.04-1.22)	1.07 (0.99-1.15)	1.19 (1.05-1.33)
By alcohol consumption (drinks/week)								
≤1	1.24 (1.14-1.34)	1.14 (1.04-1.24)	1.13 (1.04-1.23)	1.20 (1.09-1.31)	1.10 (1.02-1.20)	1.02 (0.94-1.11)	1.08 (1.00-1.18)	0.99 (0.87-1.11)
2-6	1.24 (1.16-1.32)	1.20 (1.12-1.29)	1.19 (1.12-1.27)	1.09 (1.02-1.17)	1.07 (1.00-1.14)	1.11 (1.04-1.19)	1.04 (0.97-1.11)	0.99 (0.90-1.09)
7+	1.19 (1.10-1.29)	1.20 (1.10-1.31)	1.13 (1.04-1.23)	1.13 (1.04-1.24)	1.08 (1.00-1.18)	1.08 (1.00-1.17)	1.09 (1.01-1.18)	1.23 (1.09-1.38)

Webtable 2: Relative risk (95% FCI/CI)* of breast cancer, by genotype for the 8 SNPs most strongly related to breast cancer risk and by 2 categories of each environmental risk factor.

	All women	Age at menarche		Parity		Age at first birth (parous women)		Age at menopause (postmenopausal never users of HRT)	
		<13	13+	Nulliparous	Parous	<25	25+	<50	50+
rs2981582									
G G	1.00 (0.95-1.05)	1.00 (0.92-1.09)	1.00 (0.94-1.07)	1.00 (0.87-1.15)	1.00 (0.95-1.06)	1.00 (0.93-1.08)	1.00 (0.92-1.08)	1.00 (0.85-1.17)	1.00 (0.88-1.14)
A G	1.28 (1.22-1.36)	1.20 (1.12-1.29)	1.31 (1.24-1.39)	1.14 (1.01-1.29)	1.29 (1.23-1.36)	1.25 (1.17-1.34)	1.33 (1.24-1.43)	1.22 (1.07-1.39)	1.33 (1.19-1.48)
A A	1.52 (1.41-1.64)	1.39 (1.23-1.56)	1.52 (1.38-1.67)	1.34 (1.08-1.67)	1.51 (1.40-1.63)	1.45 (1.30-1.62)	1.56 (1.39-1.75)	1.54 (1.24-1.92)	1.45 (1.20-1.74)
rs3803662									
G G	1.00 (0.96-1.05)	1.00 (0.93-1.07)	1.00 (0.95-1.06)	1.00 (0.89-1.13)	1.00 (0.96-1.05)	1.00 (0.94-1.07)	1.00 (0.94-1.07)	1.00 (0.88-1.14)	1.00 (0.90-1.11)
A G	1.23 (1.17-1.29)	1.26 (1.16-1.35)	1.22 (1.15-1.30)	1.25 (1.09-1.43)	1.23 (1.17-1.29)	1.22 (1.13-1.30)	1.24 (1.15-1.34)	1.45 (1.26-1.67)	1.05 (0.93-1.19)
A A	1.33 (1.19-1.49)	1.60 (1.34-1.91)	1.20 (1.05-1.38)	1.65 (1.20-2.27)	1.29 (1.15-1.45)	1.31 (1.13-1.53)	1.29 (1.08-1.53)	1.39 (1.00-1.95)	1.10 (0.83-1.45)
rs13387042									
G G	1.00 (0.94-1.07)	1.00 (0.90-1.11)	1.00 (0.92-1.09)	1.00 (0.84-1.19)	1.00 (0.93-1.07)	1.00 (0.91-1.10)	1.00 (0.91-1.10)	1.00 (0.82-1.21)	1.00 (0.85-1.17)
G A	1.10 (1.05-1.15)	1.11 (1.04-1.19)	1.09 (1.03-1.15)	1.24 (1.10-1.40)	1.08 (1.03-1.13)	1.12 (1.05-1.19)	1.03 (0.96-1.10)	1.13 (0.99-1.28)	1.18 (1.05-1.31)
A A	1.33 (1.25-1.41)	1.48 (1.35-1.63)	1.24 (1.15-1.34)	1.46 (1.23-1.74)	1.32 (1.24-1.40)	1.30 (1.19-1.42)	1.31 (1.19-1.43)	1.32 (1.10-1.58)	1.35 (1.17-1.56)
rs889312									
A A	1.00 (0.96-1.05)	1.00 (0.93-1.07)	1.00 (0.95-1.06)	1.00 (0.89-1.13)	1.00 (0.95-1.05)	1.00 (0.94-1.07)	1.00 (0.93-1.07)	1.00 (0.88-1.14)	1.00 (0.90-1.11)
A C	1.14 (1.08-1.20)	1.11 (1.03-1.20)	1.17 (1.10-1.24)	1.05 (0.92-1.20)	1.17 (1.11-1.23)	1.19 (1.11-1.27)	1.15 (1.07-1.24)	1.10 (0.96-1.27)	1.17 (1.04-1.31)
C C	1.24 (1.11-1.39)	1.32 (1.11-1.57)	1.22 (1.07-1.40)	1.53 (1.14-2.06)	1.23 (1.10-1.38)	1.22 (1.05-1.43)	1.24 (1.05-1.46)	1.36 (0.98-1.89)	1.23 (0.94-1.62)
rs13281615									
A A	1.00 (0.95-1.05)	1.00 (0.92-1.09)	1.00 (0.94-1.07)	1.00 (0.86-1.16)	1.00 (0.95-1.06)	1.00 (0.93-1.08)	1.00 (0.92-1.08)	1.00 (0.86-1.17)	1.00 (0.88-1.14)
A G	1.09 (1.05-1.14)	1.13 (1.05-1.21)	1.09 (1.03-1.15)	0.94 (0.83-1.06)	1.13 (1.08-1.18)	1.16 (1.09-1.24)	1.10 (1.03-1.17)	1.07 (0.94-1.22)	1.05 (0.94-1.17)
G G	1.17 (1.09-1.26)	1.18 (1.05-1.33)	1.16 (1.05-1.27)	1.12 (0.91-1.38)	1.17 (1.08-1.27)	1.22 (1.09-1.36)	1.13 (1.00-1.27)	1.14 (0.91-1.43)	1.10 (0.91-1.33)
rs4666451									
A A	1.00 (0.92-1.09)	1.00 (0.88-1.14)	1.00 (0.90-1.11)	1.00 (0.80-1.25)	1.00 (0.92-1.09)	1.00 (0.89-1.13)	1.00 (0.88-1.13)	1.00 (0.78-1.28)	1.00 (0.82-1.22)
A G	1.05 (1.00-1.10)	0.98 (0.91-1.05)	1.08 (1.02-1.14)	1.04 (0.92-1.18)	1.05 (1.01-1.10)	1.03 (0.96-1.09)	1.09 (1.01-1.16)	1.19 (1.04-1.36)	1.01 (0.90-1.13)
G G	1.16 (1.10-1.22)	1.18 (1.09-1.28)	1.11 (1.04-1.19)	1.18 (1.02-1.35)	1.15 (1.09-1.21)	1.09 (1.02-1.18)	1.20 (1.11-1.30)	1.28 (1.11-1.49)	1.02 (0.90-1.15)
rs981782									
C C	1.00 (0.93-1.07)	1.00 (0.90-1.11)	1.00 (0.92-1.09)	1.00 (0.83-1.21)	1.00 (0.93-1.07)	1.00 (0.91-1.10)	1.00 (0.90-1.11)	1.00 (0.81-1.24)	1.00 (0.84-1.19)
A C	1.02 (0.98-1.07)	1.11 (1.04-1.19)	0.99 (0.94-1.05)	1.01 (0.90-1.14)	1.05 (1.00-1.09)	1.03 (0.96-1.10)	1.06 (0.99-1.13)	1.32 (1.16-1.50)	0.91 (0.82-1.01)
A A	1.13 (1.07-1.20)	1.15 (1.05-1.26)	1.13 (1.05-1.21)	0.94 (0.80-1.10)	1.16 (1.09-1.23)	1.15 (1.06-1.25)	1.17 (1.07-1.28)	1.34 (1.14-1.57)	0.99 (0.86-1.14)
rs1045485†									
C C & C G	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
G G	1.07 (0.99-1.14)	1.07 (0.95-1.20)	1.08 (0.98-1.18)	1.08 (0.89-1.32)	1.07 (0.99-1.15)	1.09 (0.98-1.21)	1.04 (0.93-1.16)	1.03 (0.83-1.28)	1.04 (0.87-1.24)

Webtable 2 (continued): Relative risk (95% FCI/CI)* of breast cancer, by genotype for the 8 SNPs most strongly related to breast cancer risk and by 2 categories of each environmental risk factor.

	All women	HRT use (postmenopausal women)		Body mass index (kg/m ²)		Height (cm)		Alcohol consumption (drinks/day)	
		Never/past	Current	<25	25+	<165	165+	<1	1+
rs2981582									
G G	1.00 (0.95-1.05)	1.00 (0.92-1.08)	1.00 (0.92-1.09)	1.00 (0.93-1.08)	1.00 (0.93-1.08)	1.00 (0.93-1.07)	1.00 (0.92-1.08)	1.00 (0.94-1.06)	1.00 (0.91-1.10)
A G	1.28 (1.22-1.36)	1.30 (1.22-1.40)	1.25 (1.16-1.34)	1.21 (1.13-1.29)	1.33 (1.25-1.41)	1.24 (1.17-1.32)	1.31 (1.23-1.40)	1.31 (1.25-1.38)	1.17 (1.08-1.27)
A A	1.52 (1.41-1.64)	1.50 (1.33-1.68)	1.38 (1.22-1.55)	1.50 (1.35-1.66)	1.46 (1.32-1.63)	1.42 (1.29-1.57)	1.57 (1.40-1.75)	1.50 (1.37-1.64)	1.44 (1.26-1.65)
rs3803662									
G G	1.00 (0.96-1.05)	1.00 (0.94-1.07)	1.00 (0.93-1.07)	1.00 (0.94-1.06)	1.00 (0.94-1.06)	1.00 (0.95-1.06)	1.00 (0.94-1.07)	1.00 (0.95-1.05)	1.00 (0.92-1.08)
A G	1.23 (1.17-1.29)	1.22 (1.13-1.31)	1.21 (1.12-1.32)	1.24 (1.16-1.33)	1.23 (1.15-1.31)	1.25 (1.17-1.33)	1.22 (1.13-1.31)	1.25 (1.18-1.32)	1.19 (1.09-1.30)
A A	1.33 (1.19-1.49)	1.32 (1.11-1.56)	1.27 (1.06-1.51)	1.38 (1.19-1.61)	1.29 (1.10-1.52)	1.34 (1.16-1.55)	1.31 (1.11-1.54)	1.27 (1.12-1.45)	1.46 (1.19-1.78)
rs13387042									
G G	1.00 (0.94-1.07)	1.00 (0.90-1.11)	1.00 (0.90-1.11)	1.00 (0.91-1.10)	1.00 (0.91-1.10)	1.00 (0.92-1.09)	1.00 (0.91-1.10)	1.00 (0.93-1.08)	1.00 (0.89-1.13)
G A	1.10 (1.05-1.15)	1.17 (1.09-1.25)	1.04 (0.97-1.12)	1.09 (1.03-1.16)	1.10 (1.03-1.17)	1.11 (1.05-1.18)	1.07 (1.00-1.14)	1.11 (1.05-1.17)	1.07 (0.99-1.16)
A A	1.33 (1.25-1.41)	1.37 (1.25-1.50)	1.27 (1.15-1.40)	1.33 (1.22-1.45)	1.33 (1.23-1.45)	1.30 (1.21-1.41)	1.37 (1.25-1.50)	1.36 (1.27-1.46)	1.26 (1.13-1.41)
rs889312									
A A	1.00 (0.96-1.05)	1.00 (0.93-1.07)	1.00 (0.93-1.08)	1.00 (0.94-1.06)	1.00 (0.94-1.06)	1.00 (0.94-1.06)	1.00 (0.94-1.07)	1.00 (0.95-1.05)	1.00 (0.92-1.08)
A C	1.14 (1.08-1.20)	1.15 (1.07-1.24)	1.08 (1.00-1.17)	1.16 (1.09-1.25)	1.13 (1.06-1.21)	1.20 (1.13-1.28)	1.09 (1.01-1.17)	1.14 (1.08-1.21)	1.16 (1.06-1.27)
C C	1.24 (1.11-1.39)	1.26 (1.06-1.49)	1.17 (0.98-1.39)	1.29 (1.11-1.50)	1.26 (1.09-1.46)	1.31 (1.14-1.50)	1.22 (1.03-1.43)	1.27 (1.12-1.43)	1.24 (1.02-1.50)
rs13281615									
A A	1.00 (0.95-1.05)	1.00 (0.92-1.08)	1.00 (0.92-1.09)	1.00 (0.93-1.08)	1.00 (0.93-1.08)	1.00 (0.93-1.07)	1.00 (0.92-1.08)	1.00 (0.94-1.06)	1.00 (0.91-1.10)
A G	1.09 (1.05-1.14)	1.09 (1.02-1.17)	1.09 (1.01-1.17)	1.08 (1.02-1.15)	1.12 (1.05-1.19)	1.11 (1.05-1.18)	1.08 (1.01-1.16)	1.10 (1.05-1.16)	1.10 (1.01-1.19)
G G	1.17 (1.09-1.26)	1.08 (0.96-1.21)	1.27 (1.12-1.43)	1.16 (1.04-1.29)	1.21 (1.09-1.34)	1.19 (1.08-1.32)	1.13 (1.01-1.26)	1.16 (1.07-1.27)	1.18 (1.03-1.35)
rs4666451									
A A	1.00 (0.92-1.09)	1.00 (0.88-1.14)	1.00 (0.88-1.14)	1.00 (0.89-1.12)	1.00 (0.89-1.12)	1.00 (0.90-1.11)	1.00 (0.89-1.13)	1.00 (0.91-1.10)	1.00 (0.87-1.16)
A G	1.05 (1.00-1.10)	1.13 (1.05-1.21)	1.06 (0.98-1.14)	1.09 (1.02-1.16)	1.01 (0.95-1.08)	1.01 (0.96-1.08)	1.12 (1.05-1.20)	1.07 (1.01-1.12)	1.04 (0.96-1.13)
G G	1.16 (1.10-1.22)	1.22 (1.13-1.32)	1.16 (1.06-1.26)	1.13 (1.05-1.21)	1.18 (1.10-1.27)	1.12 (1.05-1.20)	1.23 (1.14-1.33)	1.16 (1.09-1.23)	1.17 (1.06-1.28)
rs981782									
C C	1.00 (0.93-1.07)	1.00 (0.90-1.11)	1.00 (0.90-1.12)	1.00 (0.91-1.10)	1.00 (0.91-1.10)	1.00 (0.91-1.09)	1.00 (0.90-1.11)	1.00 (0.92-1.08)	1.00 (0.88-1.13)
A C	1.02 (0.98-1.07)	1.05 (0.98-1.12)	1.05 (0.97-1.12)	1.04 (0.98-1.11)	1.07 (1.01-1.14)	1.06 (1.00-1.12)	1.04 (0.97-1.11)	1.04 (0.99-1.09)	1.07 (0.99-1.16)
A A	1.13 (1.07-1.20)	1.10 (1.01-1.20)	1.18 (1.07-1.30)	1.09 (1.01-1.18)	1.18 (1.09-1.28)	1.14 (1.06-1.23)	1.11 (1.02-1.20)	1.12 (1.05-1.19)	1.19 (1.07-1.32)
rs1045485†									
C C & C G	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
G G	1.07 (0.99-1.14)	0.99 (0.88-1.10)	1.13 (1.00-1.27)	1.07 (0.97-1.17)	1.05 (0.95-1.16)	1.03 (0.94-1.13)	1.10 (0.99-1.23)	1.00 (0.92-1.09)	1.26 (1.11-1.44)

*Floating confidence intervals (FCI) were calculated whenever relative risks for 3 genotypes were calculated so that valid comparisons can be made across any two genotypes (for details see Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med. 1991 10:1025-35).

†For rs1045485, the CC variant is infrequent (occurring in 1.6% of the population, see figure 2) and so results are given for CC & CG together; since only 2 groups are compared 95% CIs are given for GG vs CC and CG.

