Epigenetic Risks Factors in Women with Breast Cancer: A Family Case-Control Study

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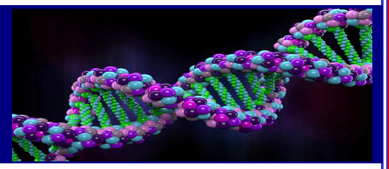


Objective

To examine the association of epigenetic risk factors - methylenetetrahydrofolate reductase (MTHFR) & health behaviors with breast cancer (BC).

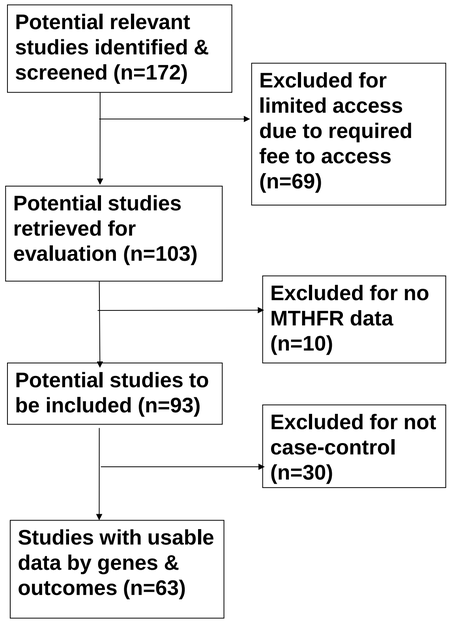
Background

- BC - 2nd leading cause of cancer death among women in the US.
- MTHFR - one of the most studied low penetrant genes involved in DNA methylation & BC.
- Health behaviors - folate intake, alcohol intake, & smoking affect methylation pathways.
- No meta-analysis has been published on MTHFR, health behaviors, & BC.

Methods

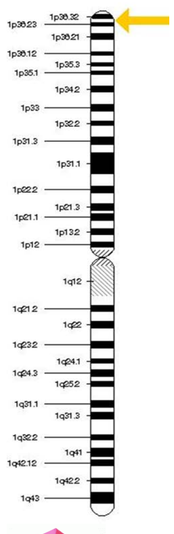
On-line databases were searched from PubMed.

Progression of Meta-Analyses – Selection of Case-Control Studies



Results

MTHFR Cytogenetic Location: 1p36.3 Chromosome 1



Pooled Relative Risk of MTHFR 677 & 1298 Genotypes

MTHFR Genotypes (# of studies)		Case n (%)	Control n (%)	RR (95% CI)
677CC	Overall (63)	13,024 (44.2)	14,874 (45.5)	0.98 (0.96 to 1)
	White (26)	5,935 (44.4)	5,958 (45.9)	0.99 (0.96 to 1.02)
	American-Mixed (14)	3,624 (42.4)	4,682 (44.1)	0.97 (0.94 to 1)
	Asian (23)	3,465 (45.9)	4,234 (46.5)	0.98 (0.95 to 1.03)
677CT	Overall (63)	12,712 (43.2)	14,008 (42.8)	1 (0.98 to 1.03)
	White (26)	5,918 (44.3)	5,638 (43.4)	1 (0.96 to 1.05)
	American-Mixed (14)	3,711 (43.4)	4,578 (43.2)	1.01 (0.96 to 1.06)
	Asian (23)	3,083 (40.9)	3,792 (41.6)	0.99 (0.96 to 1.03)
677TT	Overall (63)	3,723 (12.6)	3,819 (11.7)	1.08** (1.02 to 1.16)
	White (26)	1,513 (11.3)	1,392 (10.7)	1.1 (0.97 to 1.25)
	American-Mixed (14)	1,211 (14.2)	1,345 (12.7)	1.1** (1.02 to 1.18)
	Asian (23)	999 (13.2)	1,082 (11.9)	1.08 * (0.99 to 1.17)
Total	Overall	29,459 (100)	32,701 (100)	
	White	13,366 (100)	12,988 (100)	
	American-Mixed	8,546 (100)	10,605 (100)	
	Asian	7,547 (100)	9,108 (100)	

CI = Confidence Interval; *P* values = * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

MTHFR Genotypes (# of studies)		Case n (%)	Control n (%)	RR (95% CI)
1298AA	Overall (36)	9,584 (52.3)	11,122 (52.5)	1.01 (0.98 to 1.04)
	White (12)	3,051 (46.5)	3,472 (47.3)	0.98 (0.93 to 1.04)
	American-Mixed (10)	3,573 (51.7)	4,407 (52.7)	1.01 (0.98 to 1.04)
	Asian (14)	2,960 (61)	3,243 (59.1)	1.05 (0.99 to 1.11)
1298AC	Overall (36)	7,215 (39.3)	8,331 (39.3)	0.98 (0.95 to 1.02)
	White (12)	2,852 (43.4)	3,119 (42.5)	1.03 (0.99 to 1.07)
	American-Mixed (10)	2,759 (39.9)	3,271 (39.2)	0.99 (0.95 to 1.03)
	Asian (14)	1,604 (33)	1,941 (35.4)	0.93** (0.88 to 0.98)
1298CC	Overall (36)	1,533 (8.4)	1,728 (8.2)	1.02 (0.93 to 1.13)
	White (12)	663 (10.1)	749 (10.2)	1 (0.91 to 1.11)
	American-Mixed (10)	580 (8.4)	679 (8.1)	0.98 (0.88 to 1.09)
	Asian (14)	290 (6)	300 (5.5)	1.14 (0.89 to 1.45)
Total	Overall	18,332 (100)	21,181 (100)	
	White	6,566 (100)	7,340 (100)	
	American-Mixed	6,912 (100)	8,357 (100)	
	Asian	4,854 (100)	5,484 (100)	

CI = Confidence Interval; *P* values = * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Non-alcohol Intake and Decreased BC Risk

12 studies; RR = 0.98 (95% CI = 0.96 to 0.99), $p = 0.007$

Relative risk meta-analysis plot (random effects)

Stratum	Table (xt, xc, nt, nc)					
1	449	915	95	171	Sweden, 2009	0.98 (0.93, 1.02)
2	1213	1394	657	697	Poland, 2007	0.97 (0.93, 1.02)
3	397	402	658	698	USA, 2012	1.03 (0.92, 1.15)
4	243	536	70	98	USA, 2009	0.92 (0.85, 0.98)
5	177	270	878	1602	USA, 2009	1.16 (0.98, 1.38)
6	1405	1427	1009	987	USA, 2004	0.98 (0.94, 1.03)
7	282	562	171	335	Japan, 2008	0.99 (0.91, 1.08)
8	130	248	16	37	Taiwan, 2006	1.02 (0.94, 1.10)
9	137	157	52	32	Korea, 2004	0.87 (0.78, 0.97)
10	637	662	32	20	China, 2009	0.98 (0.96, 1.00)
11	525	469	45	28	Thailand, 2010	0.98 (0.94, 1.01)
12	232	239	12	5	India, 2010	0.97 (0.93, 1.00)
					combined [random]	0.98 (0.96, 0.99)

0.5 1 2

relative risk (95% confidence interval)

Folate Intake and Decreased BC Risk

10 studies; RR = 0.92 (95% CI = 0.87 to 0.98), $p = 0.008$

Relative risk meta-analysis plot (random effects)

Stratum	Table (xt, xc, nt, nc)					
1	79	81	62	28	Australia, 2004	0.75 (0.63, 0.91)
2	444	540	1411	1589	Poland, 2007	0.94 (0.85, 1.05)
3	37	46	24	18	UK, 2001	0.84 (0.65, 1.09)
4	167	290	124	292	USA, 2009	1.15 (1.01, 1.31)
5	736	889	590	593	USA, 2005	0.93 (0.87, 0.99)
6	218	306	140	152	Brazil, 2009	0.91 (0.82, 1.01)
7	278	606	171	304	Japan, 2008	0.93 (0.85, 1.01)
8	500	593	248	163	Korea, 2004	0.85 (0.80, 0.91)
9	387	455	282	227	China, 2009	0.87 (0.80, 0.94)
10	208	342	172	320	Singapore, 2008	1.06 (0.94, 1.19)
					combined [random]	0.92 (0.87, 0.98)

0.5 1 2

relative risk (95% confidence interval)

Non-smoking and Decreased BC Risk

13 studies; RR= 0.98 (95% CI = 0.97 to 1), $p = 0.112$

Relative risk meta-analysis plot (random effects)

Stratum	Table (xt, xc, nt, nc)					
1	423	227	107	43	Slovenia, 2011	0.95 (0.89, 1.02)
2	293	604	20	22	Sweden, 2009	0.97 (0.93, 1.00)
3	110	249	20	54	Spain, 2009	1.03 (0.93, 1.12)
4	571	605	484	496	USA, 2012	0.98 (0.91, 1.06)
5	1299	1323	1115	1091	USA, 2004	0.98 (0.93, 1.03)
6	382	724	72	186	Japan, 2008	1.06 (1.00, 1.11)
7	130	271	16	14	Taiwan, 2006	0.94 (0.87, 0.99)
8	179	116	10	10	Korea, 2004	1.03 (0.97, 1.11)
9	653	677	16	5	China, 2009	0.98 (0.97, 1.00)
10	355	620	25	42	Singapore, 2008	1.00 (0.96, 1.03)
11	552	489	17	8	Thailand, 2010	0.99 (0.97, 1.01)
12	199	193	45	51	India, 2010	1.03 (0.94, 1.13)
13	29	27	6	6	India, 2008	1.01 (0.80, 1.30)
					combined [random]	0.99 (0.98, 1.00)

0.5 1 2

relative risk (95% confidence interval)

Conclusion

- Overall analysis, MTHFR 677TT increased the risk for BC.
- Subgroup analyses, increased BC risk with MTHFR 677TT for American- Mixed and Asians; while MTHFR 1298AC decreased BC risk for Asians.
- Non-alcohol intake and folate intake are protective for BC.
- Future studies are needed to investigate MTHFR and health behaviors to prevent BC.
- Family-based case-control study is proposed.