Computational prediction of microRNA networks incorporating environmental toxicity and disease etiology

Jie Li[a], Zengrui Wu[a], Feixiong Cheng[a,]*, Weihua Li[a], Guixia Liu[a], Yun Tang[a,b,]*.

[a] Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China;

[b] Key Laboratory of Cigarette Smoke, Technical Center, Shanghai Tobacco Group Co. Ltd., Shanghai 200082, China.

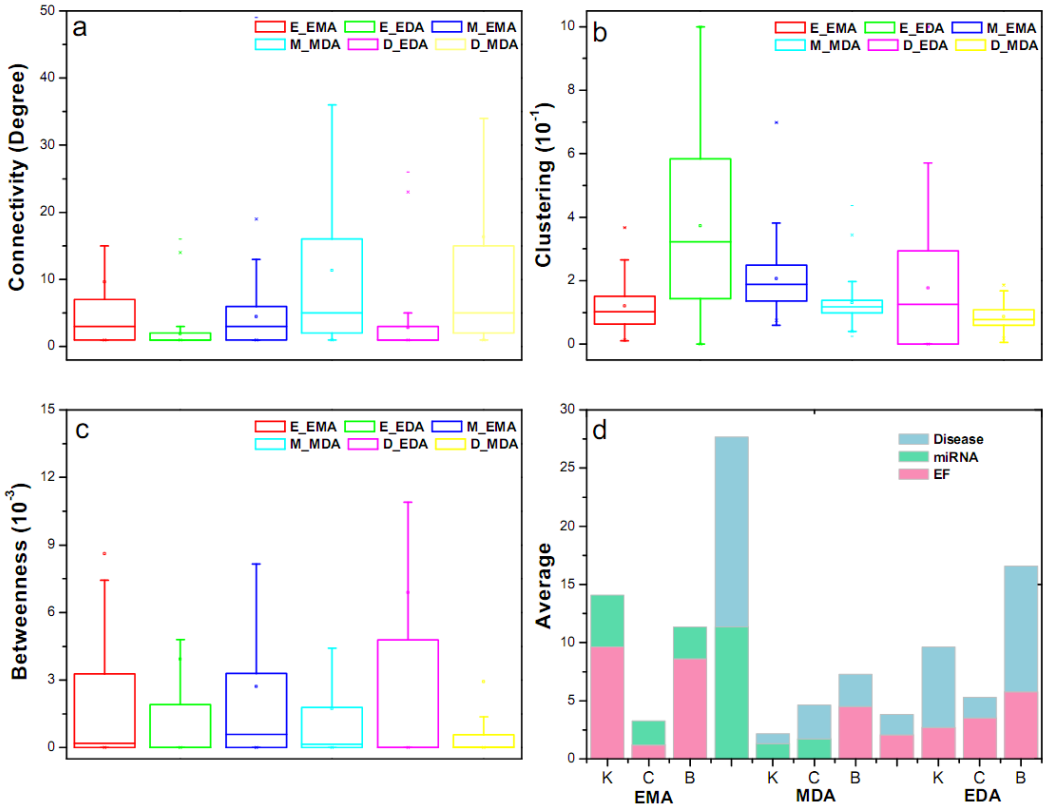
*To whom correspondence should be addressed.

Tel: +86-21-6425-1052; Fax, +86-21-6425-3651. E-mail: ytang234@ecust.edu.cn (Y. T.), fxcheng1985@gmail.com (F. C.).

Supplementary Legends:

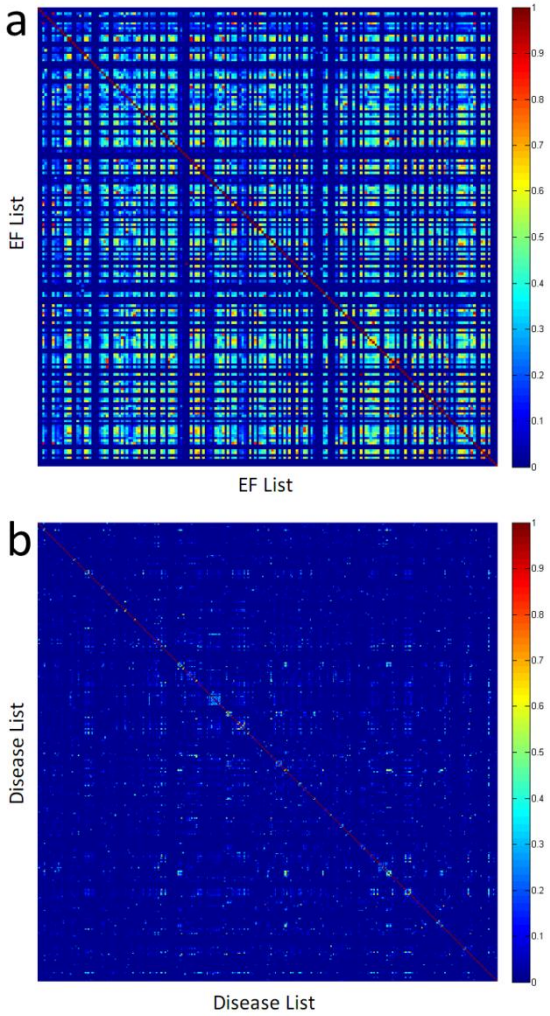
Supplementary Figure S1:

Topological features of EMA, MDA and EDA networks. Box plots show the minimum, lower quartile, median, upper quartile and the maximum about (a) connectivity distribution, (b) clustering coefficient distribution and (c) betweenness distribution. Histogram (d) explains the average topological features of three bipartite networks, where $C \times 10^{-1}$ and $B \times 10^{-3}$. EMA: EF-miRNA association; MDA: miRNA-disease association; EDA: EF-disease association. E_EMA and E_EDA are the abbreviations for EF nodes in EMA network and EDA network respectively.



Supplementary Figure S2:

Similarity hot maps of (a) EF structure Tanimoto similarity and (b) disease phenotypic similarity. Some EFs don't have exact structure information, so similarities between them and others are zero.



Supplementary Table S1:

Seen profile dataset lists.xls online

Supplementary Table S2:

Predicted list of potential EFs for breast neoplasms

ID	Name	Ref.	Known related miRNAs[a] (hsa-)
1	Radiation	1-3	mir-663, mir-638, mir-451, mir-34b, mir-125b-2, mir-9-3, mir-9-2, mir-9-1, mir-145, mir-125b-1, mir-15b, let-7i, let-7g, mir-222, mir-221, mir-214, mir-181a-1, mir-210, mir-205, mir-181a-2, mir-100, mir-31, mir-26b, mir-24-2, mir-24-1, mir-21, let-7f-2, let-7f-1, let-7e, let-7d, let-7c, let-7b, let-7a-3, let-7a-2, let-7a-1
2	Irradiation	4-6	mir-103b-2, mir-103b-1, mir-625, mir-570, mir-495, mir-452, mir-451, mir-20b, mir-148b, mir-151, mir-340, mir-374a, mir-301a, mir-299, mir-101-2, mir-29c, mir-106b, mir-128-2, mir-155, mir-195, mir-193a, mir-126, mir-145, mir-143, mir-140, mir-130a, mir-128-1, mir-15b, let-7i, let-7g, mir-222, mir-221, mir-199a-2, mir-199a-1, mir-148a, mir-16-2, mir-106a, mir-103a-1, mir-103a-2, mir-101-1, mir-96, mir-93, mir-92a-1, mir-29a, mir-27a, mir-26b, mir-24-2, mir-24-1, mir-22, mir-21, mir-20a, mir-19b-1, mir-19a, mir-18a, mir-17, mir-16-1, let-7f-2, let-7f-1, let-7a-3, let-7a-2, let-7a-1
3	Ionizing Radiation	7-9	mir-421, mir-503, mir-148b, mir-302b, mir-101-2, mir-200a, mir-29c, mir-127, mir-125a, mir-15b, let-7i, let-7g, mir-222, mir-221, mir-7-1, mir-16-2, mir-101-1, mir-100, mir-92a-2, mir-92a-1, mir-27a, mir-26b, mir-21, mir-20a, mir-19a, mir-18a, mir-17, mir-16-1, mir-15a, let-7f-2, let-7f-1, let-7e, let-7d, let-7c, let-7b, let-7a-3, let-7a-2, let-7a-1
4	Gemcitabine	10,11	mir-320e, mir-320d-2, mir-320c-2, mir-320d-1, mir-374b, mir-320b-2, mir-320c-1, mir-320b-1, mir-202, mir-409, mir-345, mir-339, mir-324, mir-326, mir-337, mir-342, mir-328, mir-374a, mir-373, mir-302c, mir-299, mir-128-2, mir-181b-2, mir-155, mir-200c, mir-320a, mir-194-1, mir-186, mir-149, mir-129-2, mir-133a-1, mir-132, mir-128-1, mir-1-2, mir-200b, mir-181a-1, mir-211, mir-205, mir-204, mir-199a-2, mir-181b-1, mir-181a-2, mir-139, mir-197, mir-29b-2, mir-29b-1, mir-26a-1, mir-24-1, mir-21, mir-16-1, let-7f-2, let-7e, let-7d, let-7c, let-7b, let-7a-1, mir-374c
5	Resveratrol	12-14	mir-663, mir-520h, mir-155, mir-146a
6	all-*trans* Retinoic Acid	15,16	mir-342, mir-181b-2, mir-152, mir-23b, mir-15b, mir-223, mir-181b-1, mir-10a, mir-16-2, mir-107, mir-23a, mir-16-1, mir-15a, let-7d, let-7c, let-7a-3, let-7a-2, let-7a-1

[a]Known EMAs were extracted from the experimentally supported dataset used and these miRNAs were verified related to breast neoplasms.

Supplementary Table S3:

Predicted list of new candidate miRNAs for breast neoplasms.

ID	Name	Validation[a]	Related EFs[b]
1	hsa-mir-142	PhenomiR	Topotecan, Irradiation
2	hsa-mir-150	PhenomiR	Cigarette Smoke (tobacco), Ppioids (morphine and heroin), BJA32515, Arsenic Trioxide (ATO)
3	hsa-mir-19b-2	PhenomiR	5-fluorouracil (5-FU)
4	hsa-mir-372	PhenomiR	Gemcitabine, BJA32515, Arsenic Trioxide (ATO)
5	hsa-mir-181d	PhenomiR	Cigarette Smoke (tobacco), Imatinib, Epigallocatechin Gallate (EGCG), Arsenic Trioxide (ATO), Docetaxel
6	hsa-mir-196b	PhenomiR	Hepatitis C Virus (HCV), Heat Stress, Imatinib, Decitabine (5-aza-2'-deoxycytidine (5-Aza-CdR))
7	hsa-mir-194-2	PhenomiR	Docetaxel
8	hsa-mir-542	[17]	anti-benzo[a]pyrene-trans-7,8-diol-9,10-epoxide, BJA32515, 17beta-estradiol (E(2)), Medroxyprogesterone Acetate, ICI-182780 and RU-486
9	hsa-mir-494	PhenomiR	Lithium, Benzo(a)pyrene (BaP), Diesel Exhaust Particles, 5-aza-2'-deoxycytidine (5-Aza-CdR) and/or Phenylbutyric acid (PBA)
10	hsa-mir-208	PhenomiR	BJA32515, Unsaturated Fatty Acids
11	hsa-mir-130b	PhenomiR	Hepatitis C Virus (HCV), Titanium and Anatase Coating (AC), Hypoxia
12	hsa-mir-708	[18]	N/A
13	hsa-mir-134	PhenomiR	Lithium and Valproate, Imatinib, 5-aza-2'-deoxycytidine (5-Aza-CdR) and/or Phenylbutyric acid (PBA), BJA32515, Etoposide (VP-16), Doxorubicin (Dox), Cisplatin (CIS)
14	hsa-mir-144	PhenomiR	Irradiation, Ionizing Radiation, BJA32515, Arsenic Trioxide (ATO)
15	hsa-mir-212	PhenomiR	Interleukin (IL)-12, Alcohol, Imatinib, Gemcitabine, BJA32515, Arsenic Trioxide (ATO), Docetaxel
16	hsa-mir-185	PhenomiR	Irradiation, Folate, Cisplatin/Fluorouracil (CF) , 5-fluorouracil (5-FU), Cisplatin (CIS)
17	hsa-mir-363	dbDEMC	Cigarette Smoke (tobacco), Cisplatin/Fluorouracil (CF) , Benzo(a)pyrene (BaP), Arsenic Trioxide (ATO)
18	hsa-mir-32	PhenomiR	Arsenic Trioxide (ATO)
19	hsa-mir-491	PhenomiR	N/A
20	hsa-mir-28	PhenomiR	Opioids (morphine and heroin)
21	hsa-mir-370	PhenomiR	BJA32515
22	hsa-mir-184	PhenomiR	Arsenic Trioxide (ATO)
23	hsa-mir-371	PhenomiR	Docetaxel
24	hsa-mir-376a-2	dbDEMC	Irradiation, BJA32515
25	hsa-mir-95	PhenomiR	Cisplatin/Fluorouracil (CF)
26	hsa-mir-376a-1	PhenomiR	Irradiation, BJA32515
27	hsa-mir-449b	[19]	Grape Seed Proanthocyanidin, Doxorubicin (Dox), Hypoxia
28	hsa-mir-362	dbDEMC	Irradiation, Cigarette Smoke (tobacco)
29	hsa-mir-449a	PhenomiR	HDAC Inhibitor: Apicidin and TSA, Doxorubicin (Dox), Hypoxia
30	hsa-mir-502	dbDEMC	Irradiation, Docetaxel

(Continued)

ID	Name	Validation[a]	Related EFs[b]
31	hsa-mir-1224	[20]	Cocoa Proanthocyanidin, Grape Seed Proanthocyanidin
32	hsa-mir-208b	Null	BJA32515, Unsaturated Fatty Acids
33	hsa-mir-381	PhenomiR	BJA32515, Cisplatin (CIS)
34	hsa-mir-219-2	PhenomiR	N/A
35	hsa-mir-498	PhenomiR	Benzo(a)pyrene (BaP), 5-aza-2'-deoxycytidine (5-Aza-CdR) and/or Phenylbutyric acid (PBA), BJA32515
36	hsa-mir-532	dbDEMC	Cocoa Proanthocyanidin, Lipopolysaccharide (LPS), Grape Seed Proanthocyanidin
37	hsa-mir-484	PhenomiR	BJA32515
38	hsa-mir-590	dbDEMC	Irradiation
39	hsa-mir-744	[21]	Irradiation, Grape Seed Proanthocyanidin
40	hsa-mir-154	PhenomiR	Gemcitabine

[a] Validation information was firstly found in PhenomiR database[22] V2.0. Then, others left were got from dbDEMC database[23] or literatures.

[b] EFs listed here were verified altering the former miRNA expression in the dataset used.

Supplementary Table S4:

Known and top 10 predicted lists of subtype-specific EFs for luminal and basal breast cancer.[a]

Luminal Subtype		Basal Subtype	
ID	**Name**	**ID**	**Name**
1	Nutlin-3a	1	Cisplatin (CIS)
2	Tamoxifen (TAM)	2	Docetaxel
		3	Erlotinib
1	Diethylstilbestrol	1	Paclitaxel (Taxol)
2	Etoposide (VP-16)	2	Radiation
3	17beta-estradiol (E2)	3	Gemcitabine
4	Adverse Drug Reaction （ADR）	4	Doxorubicin (Dox)
5	Progestin	5	Platinum
6	Docetaxel	6	Irradiation
7	Letrozole	7	Vincristine (VCR)
8	Doxorubicin (Dox)	8	Necitumumab
9	Fulvestrant （ICI-182780）	9	Curcumin
10	Trastuzumab	10	Alcohol

[a] The predicted lists here were obtained using the NBI algorithm.

Supplementary Table S5:

Predicted list of potential miRNAs for tobacco smoke related EFs.

Name	ID	miRNA	Known related diseases[a]
Tobacco	1	hsa-mir-155	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	2	hsa-mir-221	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	3	hsa-let-7a-1	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	4	hsa-mir-126	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	5	hsa-mir-27a	Gastric Neoplasms, Neoplasms
Nicotine	1	hsa-mir-26a-1	Lung Neoplasms
	2	hsa-mir-26a-2	Lung Neoplasms
	3	hsa-mir-181b-1	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	4	hsa-mir-181b-2	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	5	hsa-mir-181a-2	Gastric Neoplasms, Neoplasms, Lung Neoplasms
Benzo(a)pyrene (BaP)	1	hsa-mir-21	Epithelial-Mesenchymal Transition （EMT）, Gastric Neoplasms, Neoplasms, Lung Neoplasms, Poor Fetal Outcome
	2	hsa-let-7a-1	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	3	hsa-let-7a-2	Gastric Neoplasms, Neoplasms, Lung Neoplasms
	4	hsa-let-7a-3	Gastric Neoplasms, Neoplasms, Lung Neoplasms

[a] Diseases listed here were verified related to the former miRNA, whose expression were predicted changed by cigarette smoke related EFs.

Supplementary Table S6:

Predicted list of new candidate diseases for tobacco smoke related EFs.

Name	ID	Disease	Known related miRNAs[a](hsa-)
Tobacco	1	Glioblastoma	mir-181d, mir-146b, mir-128-2, mir-146a, mir-125b-2, mir-128-1, mir-125b-1, mir-200b, mir-205, mir-34a, mir-10b, mir-10a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	2	Immune Response	mir-146a, mir-125b-2, mir-125b-1, mir-10a
	3	Neoplasms	mir-320e, mir-320d-2, mir-320c-2, mir-320d-1, mir-320b-2, mir-320c-1, mir-320b-1, mir-498, mir-494, mir-493, mir-18b, mir-362, mir-200c, mir-320a, mir-150, mir-146a, mir-129-2, mir-125b-2, mir-130a, mir-125b-1, mir-200b, mir-205, mir-34a, mir-10b, mir-10a, mir-129-1, mir-99a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-363, mir-106b, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	4	Carcinoma, Hepatocellular	mir-320e, mir-320d-2, mir-320c-2, mir-320d-1, mir-320b-2, mir-320c-1, mir-320b-1, mir-500a, mir-498, mir-181d, mir-493, mir-146b, mir-18b, mir-338, mir-365-2, mir-365-1, mir-362, mir-200c, mir-320a, mir-150, mir-146a, mir-129-2, mir-125b-2, mir-130a, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-218-1, mir-205, mir-199b, mir-34a, mir-10b, mir-10a, mir-129-1, mir-99a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-106b, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	5	Breast Neoplasms	mir-320e, mir-320d-2, mir-320c-2, mir-320d-1, mir-320b-2, mir-320c-1, mir-320b-1, mir-638, mir-625, mir-500a, mir-493, mir-146b, mir-18b, mir-338, mir-337, mir-365-2, mir-365-1, mir-128-2, mir-200c, mir-320a, mir-146a, mir-129-2, mir-125b-2, mir-130a, mir-128-1, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-218-1, mir-205, mir-199b, mir-34a, mir-10b, mir-10a, mir-129-1, mir-99a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-106b, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
Nicotine	1	Colonic Neoplasms	mir-498, mir-493, mir-365-2, mir-365-1, mir-128-2, mir-200c, mir-146a, mir-125b-2, mir-128-1, mir-125b-1, mir-200b, mir-223, mir-205, mir-34a, mir-10b, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-106b, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	2	Leukemia	mir-18b, mir-125b-2, mir-130a, mir-125b-1, mir-223, mir-199b, mir-34a, mir-99a, mir-92a-2, mir-92a-1, mir-31, mir-20a, mir-18a, mir-15a, mir-16-2, mir-21, mir-17, mir-16-1
	3	Carcinoma, Non-Small-Cell Lung	mir-625, mir-146b, mir-337, mir-200c, mir-146a, mir-125b-2, mir-130a, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-218-1, mir-205, mir-199b, mir-34a, mir-30a, mir-15a, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	4	Carcinoma, Hepatocellular	mir-320e, mir-320d-2, mir-320c-2, mir-320d-1, mir-320b-2, mir-320c-1, mir-320b-1, mir-500a, mir-498, mir-181d, mir-493, mir-146b, mir-18b, mir-338, mir-365-2, mir-365-1, mir-362, mir-200c, mir-320a, mir-150, mir-146a, mir-129-2, mir-125b-2, mir-130a, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-218-1, mir-205, mir-199b, mir-34a, mir-10b, mir-10a, mir-129-1, mir-99a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-106b, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	5	Glioblastoma	mir-181d, mir-146b, mir-128-2, mir-146a, mir-125b-2, mir-128-1, mir-125b-1, mir-200b, mir-205, mir-34a, mir-10b, mir-10a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1

(Continued)

Name	ID	Disease	Known related miRNAs[a](hsa-)
Benzo(a)pyrene (BaP)	1	Breast Neoplasms	mir-320e, mir-320d-2, mir-320c-2, mir-320d-1, mir-320b-2, mir-320c-1, mir-320b-1, mir-638, mir-625, mir-500a, mir-493, mir-146b, mir-18b, mir-338, mir-337, mir-365-2, mir-365-1, mir-128-2, mir-200c, mir-320a, mir-146a, mir-129-2, mir-125b-2, mir-130a, mir-128-1, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-218-1, mir-205, mir-199b, mir-34a, mir-10b, mir-10a, mir-129-1, mir-99a, mir-92a-2, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-15a, mir-106b, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	2	Lung Neoplasms	mir-638, mir-494, mir-146b, mir-18b, mir-338, mir-365-2, mir-365-1, mir-128-2, mir-200c, mir-150, mir-146a, mir-130a, mir-128-1, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-205, mir-199b, mir-34a, mir-10b, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-106b, mir-106a, mir-21, mir-17
	3	Carcinoma, Non-Small-Cell Lung	mir-625, mir-146b, mir-337, mir-200c, mir-146a, mir-125b-2, mir-130a, mir-125b-1, mir-200b, mir-223, mir-218-2, mir-218-1, mir-205, mir-199b, mir-34a, mir-30a, mir-15a, mir-16-2, mir-106a, mir-21, mir-17, mir-16-1
	4	Ovarian Neoplasms	mir-625, mir-181d, mir-146b, mir-338, mir-200c, mir-320a, mir-146a, mir-125b-2, mir-130a, mir-125b-1, mir-200b, mir-223, mir-218-1, mir-34a, mir-99a, mir-92a-1, mir-31, mir-30a, mir-20a, mir-18a, mir-106b, mir-21, mir-17, mir-16-1

[a]miRNAs listed here were those related to the former disease and could be altered by cigarette smoke related EFs.

References for Supplementary Information:

1. Preston, D. L. *et al.* Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res* **158**, 220-235 (2002).
2. Boice Jr, J. D., Land, C. E., Shore, R. E., Norman, J. E. & Tokunaga, M. Risk of breast cancer following low-dose radiation exposure 1. *Radiology* **131**, 589-597 (1979).
3. Nguyen, D. H. *et al.* Radiation acts on the microenvironment to affect breast carcinogenesis by distinct mechanisms that decrease cancer latency and affect tumor type. *Cancer Cell* **19**, 640-651 (2011).
4. Clemons, M., Loijens, L. & Goss, P. Breast cancer risk following irradiation for hodgkin's disease. *Cancer Treat Rev* **26**, 291-302 (2000).
5. Adams, M. J. *et al.* Breast cancer risk 55+ years after irradiation for an enlarged thymus and its implications for early childhood medical irradiation today. *Cancer Epidem Biomar* **19**, 48-58 (2010).
6. Modan, B., Alfandary, E., Chetrit, A. & Katz, L. Increased risk of breast cancer after low-dose irradiation. *Lancet* **333**, 629-631 (1989).
7. Hu, J. J., Smith, T. R., Miller, M. S., Lohman, K. & Case, L. D. Genetic regulation of ionizing radiation sensitivity and breast cancer risk. *Environ Mol Mutagen* **39**, 208-215 (2002).
8. Land, C. E., Boice, J. D., Shore, R. E., Norman, J. E. & Tokunaga, M. Breast cancer risk from low-dose exposures to ionizing radiation: Results of parallel analysis of three exposed populations of women. *J Nat Cancer I* **65**, 353-376 (1980).
9. Millikan, R. C., Player, J. S., deCotret, A. R., Tse, C. K. & Keku, T. Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. *Cancer Epidem Biomar* **14**, 2326-2334 (2005).
10. Li, Y. W. *et al.* Up-regulation of *miR-200* and *let-7* by natural agents leads to the reversal of epithelial-to-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. *Cancer Res* **69**, 6704-6712 (2009).
11. Dent, S., Messersmith, H. & Trudeau, M. Gemcitabine in the management of metastatic breast cancer: A systematic review. *Breast Cancer Res Tr* **108**, 319-331 (2008).
12. Athar, M. *et al.* Resveratrol: A review of preclinical studies for human cancer prevention. *Toxicol Appl Pharm* **224**, 274-283 (2007).
13. Tili, E. *et al.* Resveratrol decreases the levels of miR-155 by upregulating miR-663, a microRNA targeting *JunB* and *JunD*. *Carcinogenesis* **31**, 1561-1566 (2010).
14. Tili, E. & Michaille, J. J. Resveratrol, microRNAs, inflammation, and cancer. *J Nucleic Acids* **2011**, 102431 (2011).
15. Bryan, M. *et al.* A pilot phase II trial of *all-trans* retinoic acid (Vesanoid) and paclitaxel (Taxol) in patients with recurrent or metastatic breast cancer. *Invest New Drug* **29**, 1482-1487 (2011).
16. Rahim, R. & Strobl, J. S. Hydroxychloroquine, chloroquine, and *all-trans* retinoic acid regulate growth, survival, and histone acetylation in breast cancer cells. *Anti-cancer Drug* **20**, 736-745 (2009).
17. Dvinge, H. *et al.* The shaping and functional consequences of the microRNA landscape in breast cancer. *Nature* **497**, 378-382 (2013).
18. Ryu, S. *et al.* Suppression of miRNA-708 by polycomb group promotes metastases by calcium-induced cell migration. *Cancer Cell* **23**, 63-76 (2013).
19. Hannafon, B. N., Sebastiani, P., de Las Morenas, A., Lu, J. & Rosenberg, C. L. Expression of microRNA and their gene targets are dysregulated in preinvasive breast cancer. *Breast Cancer Res* **13**, R24 (2011).
20. Shah, M. Y., Pan, X., Fix, L. N., Farwell, M. A. & Zhang, B. 5-fluorouracil drug alters the microrna expression profiles in MCF-7 breast cancer cells. *J Cell Physiol* **226**, 1868-1878 (2011).
21. Leivonen, S. K. *et al.* High-throughput screens identify microRNAs essential for HER2 positive breast cancer cell growth. *Mol Oncol* **8**, 93-104(2014).

22. Ruepp, A. *et al.* PhenomiR: a knowledgebase for microRNA expression in diseases and biological processes. *Genome Biol* **11**, R6 (2010).
23. Yang, Z. *et al.* dbDEMC: a database of differentially expressed miRNAs in human cancers. *BMC Genomics* **11**, S5 (2010).