Published in final edited form as:

Cancer Causes Control. 2008 December ; 19(10): 1139–1145. doi:10.1007/s10552-008-9181-2.

Family history of malignancies and risk of breast cancer: prospective data from the Shanghai women's health study

Briseis A. Kilfoy,

School of Epidemiology and Public Health, Yale University, 60 College Street, LEPH 440, P.O. Box 208034, New Haven, CT 06520-8034, USA

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

Yawei Zhang,

School of Epidemiology and Public Health, Yale University, 60 College Street, LEPH 440, P.O. Box 208034, New Haven, CT 06520-8034, USA

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

Xiao-Ou Shu,

Center for Health Services Research, Department of Medicine, Vanderbilt University, Nashville, TN, USA

Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, USA

Yu-Tang Gao,

Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People's Republic of China

Bu-Tian Ji,

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

Gong Yang,

Center for Health Services Research, Department of Medicine, Vanderbilt University, Nashville, TN, USA

Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, USA

Hong Lan Li,

Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People's Republic of China

Nathaniel Rothman,

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

Wong-Ho Chow, and

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD, USA

Wei Zheng

Center for Health Services Research, Department of Medicine, Vanderbilt University, Nashville, TN, USA

Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, USA

Abstract

A population-based cohort study was conducted in Shanghai, China, to investigate the relationship between family cancer history in first-degree relatives and risk of breast cancer. A total of 570 newly diagnosed breast cancer patients were identified from the cohort of 73,222 women during the follow-up period. Breast cancer risk was elevated (RR = 1.74, 95% CI: 1.10–2.73) for those with a family history of breast cancer and the risk was stronger for women who were younger than 55 years (RR = 2.07, 95% CI: 1.17–3.64). In addition, a significantly increased risk was observed for women with a family history of leukemia (RR = 2.06; 95% CI: 1.02–4.15) and among younger women, those who reported having a family history of any cancer (RR = 1.41, 95% CI: 1.10–1.82), lung cancer (RR = 1.72, 95% CI: 1.12–2.65), and esophageal cancer (RR = 2.99, 95% CI: 1.62–5.51). This cohort study suggests that, as previously observed in high risk populations, *family history* plays an important role in breast cancer also in a low risk population. The link between breast cancer risk and family history of cancers of the lung and esophagus, as well as leukemia, warrants further investigation.

Keywords

Family history; Breast cancer

Introduction

Breast cancer is the most common malignancy among women in the United States and most other Western countries [3]. The incidence rates, are on average, three times lower in less developed countries [20, 33]. In China, breast cancer incidence is nearly six times lower than in the United States, but the incidence rate has increased substantially from 1987 to 1999 [40]. Shanghai, the largest industrial city on the east coast of China, demonstrated a 40% increase in breast cancer incidence from 1975 (19.6 per 100,000) to 1997 (27.2 per 100,000) [14, 33]. Changing environmental exposures are likely to have contributed to the increase in breast cancer incidence in China [33].

On the other hand, family history is well-recognized as a strong risk factor for female breast cancer [9, 11, 17, 22, 26, 28]. Most previous studies have shown that having a first-degree relative with breast cancer approximately doubles the risk of the disease [2, 6, 9, 11, 22, 26–28, 32, 34], although the relative risk estimates range from 1.2 to 8.8 [5, 19, 38]. However, the relationship between family history of other malignancies and the risk of breast cancer is unclear.

The Shanghai Women's Health Study (SWHS) is a prospective, population-based cohort study with detailed questions on environmental risk factors and family cancer history. To the extent that the relative contributions of environment and genetic predisposition may differ among populations, exploring these risk factors in this low-risk population may provide new insights into the etiology of breast cancer. Herein, we examine the role of family cancer history in relation to breast cancer risk.

Methods

Study population

A detailed description of SWHS population has been published elsewhere [41]. Briefly, a roster of 81,170 women aged 40–70 years was obtained from the resident offices in seven communities located in urban Shanghai, China. A total of 75,221 (92.7%) women participated in the study and completed baseline surveys between 1996 and 2000. Of these women, we excluded 279 who were found to be younger than age 40 or older than age 70 years and 1,490 women who had various malignancies at the baseline interview, and 10 women who were diagnosed as cancer patients within one month after the baseline interview from the cohort. The remaining cohort of 73,222 women was followed through December 2005.

Follow-up and data collection

The first follow-up interview was conducted in 2000–2002, the second was conducted in 2002–2004, and the third follow-up interview was conducted from 2004 to 2007. A standardized and structured questionnaire was used to update information on environmental and lifestyle factors, as well as interim health history, including cancer, cardiovascular disease, stroke, bone fracture, and other chronic diseases. Incident cancer cases were also ascertained through the Shanghai Cancer Registry, which is legally mandated in Shanghai, China. Information on date of diagnosis and hospital location was collected. Medical charts and pathology slides were collected from diagnostic hospital to verify the cancer diagnosis. For subjects who had moved, the new address was requested from the neighborhood Community Office, local police department, or the Shanghai Resident Registry. Death certificate data from the Shanghai Vital Statistics Unit was collected to identify causes of death.

Information on family cancer history in first-degree relatives was collected during the baseline survey. Each subject was asked to report whether their family members, including parents, siblings and children, had ever been diagnosed with cancer, if so, further information was obtained on which family member, what type of cancer, and when the cancer was diagnosed. In addition, information on demographic factors, active and passive smoking, dietary intakes, and other exposures were collected in the baseline survey.

Statistical analysis

Person-years for each subject were calculated from the date of enrollment to the primary endpoint (diagnosis of cancer), death, or December 31, 2005, whichever came first. Cox proportional hazard models were employed to compute the incidence rate ratios (RR). Potential confounding variables, including age, education, number of siblings, age at menarche, menopausal status, parity, and age at first birth were controlled for, in the final model. Adjustment for family income, BMI, smoking, passive smoke exposure, or alcohol consumption did not result in material changes of the observed associations, and were therefore not included in the final model. Women who reported having no family members with any cancers were treated as the reference group. All the analyses were performed in SAS 8.02 (SAS Institute Inc., Cary, NC). All tests were two-sided, with the significance level of 0.05.

Results

Compared to other women in the cohort, breast cancer patients were generally younger at the age of menarche and older at the time of first birth, and had fewer numbers of children and higher educational levels (Table 1). The distributions of age, tobacco smoking, alcohol

consumption, and menopausal status at baseline were similar in breast cancer patients and the larger cohort.

A family history of any cancer, overall, was associated with no increased risk of breast cancer (RR = 1.09, 95% CI: 0.91–1.31). However, the risk increased significantly in women having a family history of breast cancer (RR = 1.74, 95% CI: 1.10–2.73). The risk was greater when the relative affected with breast cancer was a parent (RR = 2.28, 95% CI: 1.31–3.97) than a sibling (RR = 1.23, 95% CI: 0.58–2.60). A significantly increased risk was observed in women having a family history of leukemia (RR = 2.06, 95% CI: 1.02–4.15). An elevated risk with borderline significance was also observed for those with an overall family history of cancer of the lung (RR = 1.34, 95% CI: 0.96–1.87) and bladder (RR = 2.04, 95% CI: 0.96–4.30). For lung cancer, the excess risk was restricted to those with an affected parent. The risk estimates were attenuated when cohort members who smoked were excluded from the analysis (RR = 1.10, 95% CI: 0.92–1.33 for those who reported having a first-degree relative diagnosed with lung cancer and RR = 1.77, 95% CI: 1.13–2.77 for those whose relative was diagnosed with bladder cancer) (Table 2).

When stratified by age at diagnosis of the breast cancer among cohort members (Table 3), an increased risk associated with family history was generally observed in younger women. Among women younger than 55 years of age, an increased risk of breast cancer was associated with a family history of any cancers (RR = 1.41, 95% CI: 1.10–1.82), with the excess risk mainly confined to those with an affected parent (RR = 1.54, 95% CI: 1.18–1.99). For women *younger than 55 years of age* with a family history of breast cancer, their breast cancer risk was more than two times higher than women without such a history (RR = 2.07, 95% CI: 1.17–3.64). The risk was observed for a history of breast cancer in both parents (RR = 2.35, 95% CI: 1.21–4.57) and siblings (RR = 1.54, 95% CI: 0.56–4.22). Additionally, a significant association was found for a family history of esophageal cancer overall (RR = 2.99, 95% CI: 1.62–5.51), as well as in parents (RR = 2.80, 95% CI: 1.48–5.31) and in siblings (RR = 10.2, 95% CI: 1.43–73.2). A history of lung cancer in parents (RR = 1.72; 95% CI: 1.12–2.65) was associated with an increased risk of breast cancer. Family history of bladder cancer in siblings (RR = 22.4, 95% CI: 3.11–161) was associated with an increased risk of breast cancer, but it was based on one exposed case. Among women who were aged 55 years or older, the only significant association was observed for those with a family history of leukemia in siblings (RR = 3.17; 95% CI: 1.01–9.94). Similar results were observed after excluding the patients diagnosed within the first year of follow-up (data not shown).

Discussion

Findings from the SWHS support a role for family history of cancer in the development of breast cancer, mainly in early onset breast cancers. Among women who were younger than 55 years old, the risk of breast cancer was associated with a family history of cancer overall and cancers of the breast, esophagus, and lung. We estimated that among this large population of Chinese women, about 2.2% of incident breast cancer cases could be attributable to having a family history of cancer in first-degree relatives in general, and 1.4% to having a family history of breast cancer in first-degree relatives specifically.

A number of studies have reported a positive association between breast cancer and family history of breast cancer [7, 9, 16, 18, 35]. Our results are consistent with previous findings. Two separate meta-analyses of 52 and 74 breast cancer studies demonstrated a 1.3- to 3.3-fold increased risk of breast cancer associated with having one affected first-degree relative [9, 28]. The meta-analyses also provided evidence that the magnitude of breast cancer risk typically increases with the decreasing age of the index case and increases with the report of

additional affected relatives [9, 28]. Although we were able to demonstrate a greater risk of early onset breast cancer associated with a family history of breast cancer, we did not observe a significant trend in increasing risk with the number of affected first-degree relatives. The number of cases who reported a family history of breast cancer was small in this cohort.

Family history reflects both shared genetics and environmental factors. The association between breast cancer and a family history of breast cancer observed in our study may be partially attributed to inherited genetic susceptibility. A number of genes that have been identified during the past 10 years, most notably the *BRCA1* and *BRCA2* genes, have been linked to breast carcinogenesis [1, 8, 11, 12, 26]. Mutations in *BRCA1* and *BRCA2* are associated with 10-fold or more increased risk of breast cancer [12]. Furthermore, the proportion of breast cancers in young patients accounted for, by these high risk genes is considerably higher [12]. This is consistent with our results that an increased risk associated with family history was more pronounced among younger women, indicating a stronger influence of family history in early onset breast cancer cases. Although mutation and other alterations in these genes are not common (less than 5%) [12], there is evidence that prevalence varies in the U.S. population by racial/ethnic status [21]. Asian Americans have been shown to have the lowest prevalence of *BRCA1* mutations compared to African American, Hispanic, and non-Hispanic white women [21]. However, a relatively higher prevalence of 7–8% was reported previously for Chinese women from Singapore with early onset breast cancer [36]. As such, the prevalence of predisposing mutations can be higher in populations that have lower cancer risk than in populations with overall higher risk. It is subsequently important to note that in addition to these high risk genes, other shared genetic, lifestyle, and environmental factors may also play a role in familial breast cancers.

In the SWHS, we found that a family history of cancers of the esophagus, lung, and leukemia in *first-degree relatives* was also associated with the risk of breast cancer. Two previous case-control studies have reported that family history of esophageal cancer is associated with the risk of breast cancer [10, 13], and one of the studies found that the risk was mainly seen in early onset breast cancers, which is consistent with our finding [10]. Although, no studies have reported that family history of lung cancer is associated with early onset breast cancer, two case-control studies found that non-smoking lung cancer was associated with a family history of breast cancer [25, 39]. Both lung cancer and esophageal cancer are considered to be smoking-related cancers. However, the results from previous studies of lung cancer in non-smoking populations [25], along with results from the current cohort of mainly non-smokers, do not support the notion that shared smoking exposure is responsible for the link between breast cancer risk and family history of lung and esophageal cancers. Since the risk associated with a family history of cancers of the lung and esophagus in our study was mainly seen in parents and in early onset breast cancer patients, it may indicate that certain inherited genetic susceptibility rather than shared environmental factors play an important role in the link between breast cancer and cancers of the lung and esophagus.

Breast cancer and leukemia have been linked within families that have rare germ-line mutations in either the *p53* gene (Li-Fraumeni Syndrome) [24] or ataxia telangiectasia gene [37], which support the association between family history of leukemia and breast cancer observed in the current study. Since a statistically significant increased risk was mainly seen in older breast cancer patients with siblings having leukemia, the role of environment cannot be ruled out. While no previous study has reported an association between family history of leukemia and breast cancer risk, a recent case-control study reported a positive association between family history of breast cancer and leukemia [29, 37].

In addition to family history of cancers of breast, lung, esophagus, and leukemia, family history of several other cancer types have been inconsistently linked to the risk of breast cancer. These include cancers of the colon, prostate, thyroid, gallbladder, cervix uteri, and ovary, as well as Hodgkin's disease, and non-Hodgkin lymphoma [4, 15, 23, 30, 31]. The underlying mechanisms that link breast cancer and non-breast cancers in families are currently unclear. Studies of these families may provide helpful clues for the etiology of breast cancer.

Several strengths of this study lend confidence to our findings. The prospective study design and high participation rate minimized recall and selection biases. However, information on family history of cancer was collected from subjects' recall and no further efforts have been made to contact the relatives to verify the diagnosis. Since the information was collected before the disease onset, if there is a bias resulting from subjects' inaccurate recall, it is likely to be non-differential and may result in an underestimation of the observed association. Furthermore, there is a possibility of under-reporting of family history of cancer due to under-diagnosis, limited communication about cancer in families, etc. As such, the findings are likely to be conservative. In addition, a number of comparisons have been made in this study, and chance alone may account for some of the associations.

In conclusion, the current study supports the relationship between family breast cancer history and early onset of breast cancer. The link between breast cancer and family history of cancer of the lung, esophagus, and leukemia may be due to some common genetic susceptibilities. Further studies of these families may be helpful in identifying clues to risk of both familial and sporadic breast cancer.

Acknowledgments

This research was supported by National Institutes of Health research grant R01 CA70867 and by Intramural Research Program contract N02 CP1101066. The authors express their appreciation to Shanghai residents who participated in the study and thank the research staff of the Shanghai Women's Health Study for their dedication and hard work.

References

1. Allen-Brady K, Camp NJ, Ward JH, Cannon-Albright LA. Lobular breast cancer: excess familiarity observed in the Utah Population Database. *Int J Cancer*. 2005; 117:655–661. doi:10.1002/ijc.21236. [PubMed: 15929077]
2. Ambrosone CB, Marshall JR, Vena JE, Laughlin R, Graham S, Nemoto T, Freudenheim JL. Interaction of family history of breast cancer and dietary antioxidants with breast cancer risk. *New York, United States. Cancer Causes Control*. 1995; 6:407–415. [PubMed: 8547538]
3. American Cancer Society. , editor. *Breast cancer facts and figures: 2005–2006*. ACS; Atlanta, GA: 2006.
4. Anderson H, Bladstrom A, Olsson H, Moller TR. Familial breast and ovarian cancer: a Swedish population-based register study. *Am J Epidemiol*. 2000; 152:1154–1163. doi:10.1093/aje/152.12.1154. [PubMed: 11130621]
5. Brignone G, Cusimano R, Dardanoni G, Gugliuzza M, Lanzarone F, Scibilia V, Dardanoni L. A case-control study on breast cancer risk factors in a southern European population. *Int J Epidemiol*. 1987; 16:356–361. [PubMed: 3667031]
6. Brinton LA, Daling JR, Liff JM, Schoenberg JB, Malone KE, Stanford JL, Coates RJ, Gammon MD, Hanson L, Hoover RN. Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst*. 1995; 87:827–835. [PubMed: 7791232]
7. Carpenter CL, Ross RK, Paganini-Hill A, Bernstein L. Effect of family history, obesity and exercise on breast cancer risk among postmenopausal women. *Int J Cancer*. 2003; 106:96–102. doi:10.1002/ijc.11186. [PubMed: 12794763]

8. Claus EB, Stowe M, Carter D. Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. *Breast Cancer Res Treat.* 2003; 78:7–15. doi:10.1023/A:1022147920262. [PubMed: 12611452]
9. Collaborative Group C. in Breast. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58, 209 women with breast cancer and 101, 986 women without the disease. *Lancet.* 2001; 358:1389–1399. [see comment]. doi:10.1016/S0140-6736(01)06524-2. [PubMed: 11705483]
10. Dhillon PK, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD, Mayne ST, Stanford JL, Schoenberg JB, Ahsan H, Dubrow R, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Family history of cancer and risk of esophageal and gastric cancers in the United States. *Int J Cancer.* 2001; 93:148–152. doi: 10.1002/ijc.1294. [PubMed: 11391635]
11. Easton DF. Familial risks of breast cancer. *Breast Cancer Res.* 2002; 4:179–181. doi:10.1186/bcr448. [PubMed: 12223120]
12. Eeles RA, Stratton MR, Goldgar DE, Easton DF. The genetics of familial breast cancer and their practical implications. *Eur J Cancer.* 1994; 30A:1383–1390. doi:10.1016/0959-8049(94)90190-2. [PubMed: 7999429]
13. Garavello W, Negri E, Talamini R, Levi F, Zambon P, Dal Maso L, Bosetti C, Franceschi S, La Vecchia C. Family history of cancer, its combination with smoking and drinking, and risk of squamous cell carcinoma of the esophagus. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1390–1393. doi:10.1158/1055-9965.EPI-04-0911. [PubMed: 15941946]
14. Gardner KM, Ou Shu X, Jin F, Dai Q, Ruan Z, Thompson SJ, Hussey JR, Gao YT, Zheng W. Occupations and breast cancer risk among Chinese women in urban Shanghai. *Am J Ind Med.* 2002; 42:296–308. doi:10.1002/ajim.10112. [PubMed: 12271477]
15. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst.* 1994; 86:1600–1608. doi:10.1093/jnci/86.21.1600. [PubMed: 7932824]
16. Hemminki K, Czene K. Attributable risks of familial cancer from the Family-Cancer Database. *Cancer Epidemiol Biomarkers Prev.* 2002; 11:1638–1644. [PubMed: 12496055]
17. Hemminki K, Granstrom C. Familial breast cancer: scope for more susceptibility genes? *Breast Cancer Res Treat.* 2003; 82:17–22. doi:10.1023/B:BREA.0000003871.38587.8b. [PubMed: 14672399]
18. Hemminki K, Granstrom C, Czene K. Attributable risks for familial breast cancer by proband status and morphology: a nationwide epidemiologic study from Sweden. *Int J Cancer.* 2002; 100:214–219. [see comment]. doi:10.1002/ijc.10467. [PubMed: 12115572]
19. Hiatt RA, Bawol R, Friedman GD, Hoover R. Exogenous estrogen and breast cancer after bilateral oophorectomy. *Cancer.* 1984; 54:139–144. [PubMed: 6722739]
20. IARC. Cancer incidence in five continents. Vol. VIII. IARC; Lyon: 2002.
21. John EM, Miron A, Gong G, Phipps AI, Felberg A, Li FP, West DW, Whittemore AS. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. *JAMA.* 2007; 298:2869–2876. doi:10.1001/jama.298.24.2869. [PubMed: 18159056]
22. Li R, Gilliland FD, Baumgartner KB, Samet J. Family history and risk of breast cancer in hispanic and non-hispanic women: the New Mexico Women's Health Study. *Cancer Causes Control.* 2001; 12:747–753. doi:10.1023/A:1011285205870. [PubMed: 11562115]
23. Malander S, Ridderheim M, Masback A, Loman N, Kristoffersson U, Olsson H, Nilbert M, Borg A. One in 10 ovarian cancer patients carry germ line BRCA1 or BRCA2 mutations: results of a prospective study in Southern Sweden. *Eur J Cancer.* 2004; 40:422–428. doi:10.1016/j.ejca.2003.09.016. [PubMed: 14746861]
24. Malkin D. p53 and the Li-Fraumeni syndrome. *Cancer Genet Cytogenet.* 1993; 66:83–92. doi: 10.1016/0165-4608(93)90233-C. [PubMed: 8500106]
25. Mayne ST, Buenconsejo J, Janerich DT. Familial cancer history and lung cancer risk in United States nonsmoking men and women. *Cancer Epidemiol Biomarkers Prev.* 1999; 8:1065–1069. [PubMed: 10613338]

26. McCredie M, Paul C, Skegg DC, Williams S. Family history and risk of breast cancer in New Zealand. *Int J Cancer*. 1997; 73:503–507. doi:10.1002/(SICI)1097-0215(19971114)73:4<503::AID-IJC8>3.0.CO;2-3. [PubMed: 9389563]
27. Nomura AM, Kolonel LN, Hirohata T, Lee J. The association of replacement estrogens with breast cancer. *Int J Cancer*. 1986; 37:49–53. [PubMed: 3941022]
28. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer*. 1997; 71:800–809. doi:10.1002/(SICI)1097-0215(19970529)71:5<800::AID-IJC18>3.0.CO;2-B. [PubMed: 9180149]
29. Rauscher GH, Sandler DP, Poole C, Pankow J, Mitchell B, Bloomfield CD, Olshan AF. Family history of cancer and incidence of acute leukemia in adults. *Am J Epidemiol*. 2002; 156:517–526. doi:10.1093/aje/kwf075. [PubMed: 12225999]
30. Rawal R, Bertelsen L, Olsen JH. Cancer incidence in first-degree relatives of a population-based set of cases of early-onset breast cancer. *Eur J Cancer*. 2006; 42:3034–3040. doi:10.1016/j.ejca.2006.04.025. [PubMed: 16996259]
31. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, Jack E, Vesprini DJ, Kuperstein G, Abrahamson JL, Fan I, Wong B, Narod SA. Prevalence and penetrance of germ-line BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet*. 2001; 68:700–710. doi: 10.1086/318787. [PubMed: 11179017]
32. Rookus MA, van Leeuwen FE. Oral contraceptives and risk of breast cancer in women aged 20–54 years. Netherlands Oral Contraceptives and Breast Cancer Study Group. *Lancet*. 1994; 344:844–851. [see comment]. [PubMed: 7916400]
33. Shannon J, Ray R, Wu C, Nelson Z, Gao DL, Li W, Hu W, Lampe J, Horner N, Satia J, Patterson R, Fitzgibbons D, Porter P, Thomas D. Food and botanical groupings and risk of breast cancer: a case–control study in Shanghai, China. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:81–90. [PubMed: 15668480]
34. Siskind V, Schofield F, Rice D, Bain C. Breast cancer and breastfeeding: results from an Australian case–control study. *Am J Epidemiol*. 1989; 130:229–236. [PubMed: 2750724]
35. Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. *JAMA*. 1993; 270:1563–1568. see comment. doi:10.1001/jama.270.13.1563. [PubMed: 8371466]
36. Sng JH, Chang J, Feroze F. The prevalence of BRCA1 mutations in Chinese patients with early onset breast cancer and affected relatives. *Br J Cancer*. 2000; 82:538–542. doi:10.1054/bjoc.1999.0960. [PubMed: 10682662]
37. Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N Engl J Med*. 1991; 325:1831–1836. [see comment]. [PubMed: 1961222]
38. White E, Malone KE, Weiss NS, Daling JR. Breast cancer among young U.S. women in relation to oral contraceptive use. *J Natl Cancer Inst*. 1994; 86:505–514. [PubMed: 8133534]
39. Wu AH, Fontham ET, Reynolds P, Greenberg RS, Buffler P, Liff J, Boyd P, Correa P. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol*. 1996; 143:535–542. [see comment]. [PubMed: 8610670]
40. Yang L, Parkin DM, Li L, et al. Time trends in cancer mortality in China: 1987–1999. *Int J Cancer*. 2003; 106:771–783. doi: 10.1002/ijc.11300. [PubMed: 12866039]
41. Zheng W, Chow W-H, Yang G, Jin F, Rothman N, Blair A, Li H-L, Wen W, Ji B-T, Li Q, Shu X-O, Gao Y-T. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol*. 2005; 162:1123–1131. doi:10.1093/aje/kwi322. [PubMed: 16236996]

Table 1

Select characteristics of the study population

	Cohort (<i>n</i> = 73,222)		Breast cancer (<i>n</i> = 570)	
Age				
40–44	20,720	28.3	149	26.1
45–49	15,191	20.8	111	19.5
50–54	10,323	14.1	79	13.9
55–59	7,394	10.1	81	14.2
60–64	9,390	12.8	75	13.2
65+	10,204	13.9	75	13.2
Educational level				
<6 years	15,640	21.4	81	14.2
6–8 years	27,223	37.2	185	32.5
8–10 years	20,455	27.9	198	34.7
>10 years	9,891	13.5	105	18.4
Missing	13	0.02	1	0.2
Active smoking				
No	71,184	97.2	559	98.1
Yes	2,038	2.8	11	1.9
Alcohol consumption				
No	71,570	97.7	559	98.1
Yes	1,652	2.3	11	1.9
Age at Menarche				
13 or younger	16,166	22.1	143	25.1
14	15,107	20.6	126	22.1
15	15,673	21.4	123	21.6
16	13,232	18.1	95	16.7
Older than 16	13,022	17.8	83	14.6
Missing	22	0	0	0
Age at first birth				
None	2,341	3.2	23	4.0
<20	4,084	5.6	23	4.0
20–24	17,081	23.3	102	17.9
25–29	35,594	48.6	286	50.2
30–34	12,057	16.5	117	20.5
35+	1,993	2.7	18	3.2
Missing	72	0.1	1	0.2
Parity				
0	2,341	3.2	23	4.0
1	40,620	55.5	325	57.0
2	15,597	21.3	131	23.0
3	7,792	10.6	58	10.2

	Cohort (<i>n</i> = 73,222)		Breast cancer (<i>n</i> = 570)	
4	4,385	6.0	21	3.7
5+	2,487	3.4	12	2.1
Missing	79	0.1	0	0
Menopausal status				
Premenopausal	37,420	51.1	292	51.2
Postmenopausal	35,802	49.0	278	48.8

Table 2

Association between breast cancer and family history

Family history	Cases	RR ^a	95% CI
Any cancers	161	1.09	0.91–1.31
Parents	134	0.82	0.55–1.21
Siblings	39	0.96	0.68–1.33
<i>p</i> heterogeneity			0.2923
Breast	20	1.74	1.10–2.73
Parents	13	2.28	1.31–3.97
Siblings	7	1.23	0.58–2.60
<i>p</i> heterogeneity			0.1939
Esophagus	17	1.46	0.90–2.38
Parents	15	1.51	0.90–2.53
Siblings	2	1.12	0.28–4.51
<i>p</i> heterogeneity			0.9648
Stomach	28	0.84	0.57–1.24
Parents	22	0.86	0.56–1.31
Siblings	5	0.65	0.27–1.58
<i>p</i> heterogeneity			0.9515
Colonrectum	17	1.20	0.74–1.95
Parents	11	1.02	0.57–1.88
Siblings	6	1.72	0.77–3.87
<i>p</i> heterogeneity			0.9651
Liver	13	0.64	0.37–1.12
Parents	9	0.63	0.33–1.22
Siblings	4	0.65	0.24–1.75
<i>p</i> heterogeneity			0.9585
Genital	11	1.01	0.55–1.84
Parents	10	1.16	0.62–2.18
Siblings	1	0.46	0.06–3.27
<i>p</i> heterogeneity			0.9740
Lung	39	1.34	0.96–1.87
Parents	35	1.47	1.04–2.08
Siblings	4	0.75	0.28–2.01
<i>p</i> heterogeneity			0.9590
Bladder	7	2.04	0.96–4.30
Parents	5	1.69	0.70–4.08
Siblings	2	4.37	1.08–17.6
<i>p</i> heterogeneity			Na
Leukemia	8	2.06	1.02–4.15
Parents	4	2.29	0.85–6.13
Siblings	4	2.52	0.94–6.77

Family history	Cases	RR ^a	95% CI
<i>p</i> heterogeneity			0.9792

*Age was categorized as <45, 45–49, 50–54, 55–59, 60–64, and >65

^a Adjusted for age, education, age menarche, age at first birth, age at menopause, menopausal status, parity, and number of siblings and children

Table 3

Association between breast cancer and family history by age at diagnosis

Family history	< 55 years		≥55+ years	
	Cases	RR ^a (95% CI)	Cases	RR ^a (95% CI)
Any cancers	90	1.41(1.10–1.82)	71	0.82(0.62–1.07)
Parents	84	1.54(1.18–1.99)	50	0.99(0.32–3.11)
Siblings	12	0.98(0.54–1.77)	27	0.74(0.23–2.31)
<i>p</i> heterogeneity		0.2923		0.2923
Breast	14	2.07(1.17–3.64)	6	0.83(0.37–1.87)
Parents	10	2.35(1.21–4.57)	3	1.01(0.42–3.17)
Siblings	4	1.54(0.56–4.22)	3	0.71(0.23–2.24)
<i>p</i> heterogeneity		0.9912		0.0081
Esophagus	11	2.99(1.62–5.51)	6	0.75(0.33–1.69)
Parents	10	2.80(1.48–5.31)	5	0.79(0.32–1.91)
Siblings	1	10.2(1.43–73.2)	1	0.57(0.08–4.07)
<i>p</i> heterogeneity		Na		0.9744
Stomach	13	0.97(0.55–1.70)	15	0.76(0.45–1.28)
Parents	11	0.97(0.53–1.79)	11	0.80(0.44–1.47)
Siblings	2	0.81(0.20–3.30)	3	0.48(0.15–1.50)
<i>p</i> heterogeneity		0.9793		0.9740
Colonrectum	7	1.24(0.58–2.64)	10	1.14(0.60–2.16)
Parents	6	1.25(0.55–2.82)	5	0.83(0.34–2.03)
Siblings	1	1.09(0.15–7.78)	5	1.89(0.78–4.61)
<i>p</i> heterogeneity		0.9902		0.9738
Liver	7	0.82(0.38–1.74)	6	0.52(0.23–1.18)
Parents	7	0.95(0.45–2.02)	2	0.30(0.08–1.22)
Siblings	0	Na	4	0.82(0.30–2.22)
<i>p</i> heterogeneity		0.9998		0.9700
Genital	4	1.16(0.43–3.12)	7	0.97(0.45–2.05)
Parents	4	1.33(0.49–3.59)	6	1.09(0.48–2.46)
Siblings	0	Na	1	0.60(0.08–4.26)
<i>p</i> heterogeneity		1.0		0.9830
Lung	24	1.72(1.12–2.65)	15	0.90(0.53–1.53)
Parents	24	1.94(1.26–2.98)	11	0.89(0.49–1.64)
Siblings	0	Na	4	0.90(0.33–2.43)
<i>p</i> heterogeneity		0.9998		0.9671
Bladder	3	2.60(0.83–8.14)	4	1.90(0.70–5.12)
Parents	2	1.80(0.45–7.26)	3	1.79(0.57–5.62)
Siblings	1	22.4(3.11–161)	1	2.31(0.32–16.6)
<i>p</i> heterogeneity		Na		Na
Leukemia	3	1.83(0.58–5.82)	5	2.12(0.87–5.17)
Parents	2	2.07(0.50–8.60)	2	2.10(0.52–8.49)

Family history	< 55 years		≥55+ years	
	Cases	RR ^a (95% CI)	Cases	RR ^a (95% CI)
Siblings	1	1.74(0.24–12.4)	3	3.17(1.01–9.94)
<i>p</i> heterogeneity	Na		Na	

*Age was categorized as <45, 45–49, 50–54, for <55 analysis and 55–59, 60–64, and >65 for the ≤55 analysis

^a Adjusted for education, age at first birth, age at menarche, menopausal status, age at menopause, parity, and number of siblings and children