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1 **Plasma equol concentration is not associated with breast cancer and fibrocystic breast**
2 **conditions among women in Shanghai, China**

3

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24

25 **ABBREVIATIONS**

26

27 BC; breast cancer

28 BSE; breast self-examination

29 CI; confidence interval

30 FBC; fibrocystic breast condition

31 LC; liquid chromatography

32 LOQ; limit of quantification

33 MS; mass spectrometry

34 NCT; non-cancerous tissue

35 OR; odds ratio

36 STIB; Shanghai Textile Industrial Bureau

37 TR-FIA; time-resolved fluoroimmunoassay

38

39 **ABSTRACT**

40

41 Equol (a bacterial metabolite of the soy isoflavone daidzein) is produced by 30-50% of humans
42 and may be associated with health outcomes. We hypothesized that plasma equol would be
43 inversely associated with risks of fibrocystic breast conditions (FBC) and breast cancer (BC).
44 Plasma from women in a breast self-examination trial in Shanghai with BC (n=269) or FBC
45 (n=443), and age-matched controls (n=1027) was analyzed for isoflavones. Equol was grouped
46 into categories (<20, 20-<45, and \geq 45 nmol/L) and, among women with daidzein \geq 20 nmol/L,
47 the log₁₀ equol:daidzein ratio was grouped into tertiles. Where available, non-cancerous tissue
48 (NCT) adjacent to the carcinomas from women with BC were classified as non-proliferative or
49 proliferative (n=130 and 172, respectively). The lesions from women with FBC were similarly
50 classified (n=99 and 92, respectively). Odds ratios (OR) and 95% confidence intervals (CI) were
51 calculated across equol categories and tertiles of log₁₀ equol:daidzein ratio. Equol categories
52 were not associated with FBC or BC (p>0.05). For log₁₀ equol:daidzein, compared to controls
53 there were positive associations in the mid tertile for proliferative FBC (OR 2.06, 95% CI 1.08-
54 3.93), BC with proliferative NCT (OR 2.95, 95% CI 1.37-6.35), and all BC regardless of
55 histology (OR 2.37, 95% CI 1.43-3.95). However, trends in ORs with increasing plasma equol
56 values or equol:daidzein ratios were not observed (p>0.05). The results of this study do not
57 provide evidence that equol plays a role in the etiology of these breast conditions. However,
58 further work is needed to confirm or refute this conclusion.

59

60 **KEYWORDS:** breast cancer; daidzein; equol; fibrocystic changes in the breast; isoflavone;
61 nested case-control study; women

62 **1. INTRODUCTION**

63

64 Soy contains the isoflavones daidzein and genistein [1, 2], and is consumed in high amounts in
65 Asian populations [3-5] and in low amounts by Western populations [6]. Isoflavones are
66 structurally similar to mammalian estrogens [7] and research has focused primarily on their
67 effects on hormone-related conditions, including risk of breast cancer. However, associations
68 between soy or isoflavone consumption and breast cancer risk have been inconsistently observed
69 [8]. Reasons for such differences are unclear but one reason may be due to inter-individual
70 differences in isoflavone metabolism.

71

72 Gut microbiota are involved in the metabolism of daidzein to equol [9] and, following soy
73 consumption, approximately 30-50% of individuals produce equol (discussed in [10]). In vitro,
74 equol was shown to have greater biological activity than daidzein, and to have a higher effective
75 free fraction in serum than genistein and 17β -estradiol (discussed in [10]). Thus, it has been
76 suggested that individuals ability to produce equol be considered in studies assessing soy intake
77 and health [11].

78

79 Two small studies in Asian and Asian-American populations have shown, albeit non-
80 significantly, lower excretion of equol or a lower proportion of equol-producers than non-
81 producers in breast cancer cases than controls [12, 13], suggesting decreased risk of breast cancer
82 in equol-producers. Similar findings were shown in Western populations [14-16], although one
83 study initially reported an increased risk [17] that attenuated with a larger sample size [18].

84 Among Chinese immigrant women in the US, mammographic breast density (a marker of risk

85 for breast cancer) was lower (representing lower risk) in equol-producers than non-producers,
86 and when stratified on equol-producer status, isoflavone intake was inversely associated with
87 breast density among equol-producers but not non-producers [19]. Further, in a cross-sectional
88 study of predominantly White postmenopausal women in the US, there was a suggestion of a
89 favorable interaction between soy intake and equol-producer status on breast density [20].

90

91 Proliferative fibrocystic breast conditions (FBC) have been associated with increased risk of
92 breast cancer [21, 22]. We showed previously that plasma genistein and daidzein concentrations
93 were inversely associated with risk of breast cancer and benign FBC among women in Shanghai,
94 China [23]. Associations between equol and these breast conditions remains largely unknown
95 and was the focus of this study. We hypothesized that, in this same population, plasma equol
96 would also be inversely associated with risk of breast cancer and benign FBC. Our specific
97 objectives were to 1) examine associations between equol and risk of breast cancer and benign
98 FBC, and 2) examine these associations stratified by proliferative status of the lesions from
99 women with FBC and of the adjacent non-cancerous tissue of breast cancer cases. Another
100 objective was to confirm whether our previously reported inverse associations between plasma
101 genistein and daidzein concentrations and risk of breast cancer and benign FBC would remain
102 when assessed in a larger sample. We tested these objectives using a case-control study design
103 that was nested within a large trial of breast self-examination [24].

104

105

106 **2. METHODS AND MATERIALS**

107

108 **2.1 Study Population**

109

110 266,064 women (ages 30-64 years) who were current or retired employees of the Shanghai
111 Textile Industrial Bureau (STIB) were enrolled in the breast self-examination (BSE) trial
112 between October 1989 and October 1991 and followed for the development of benign and
113 malignant breast disease through July 31, 2000. Briefly, participants in this study were from two
114 nested case-control studies of benign and malignant breast conditions that were conducted
115 sequentially between September 1995 through August 1997 and between September 1997 and
116 July 2000. The overall recruitment of cases and controls has been described previously [23, 25].

117

118 The Institutional Review Board of the Fred Hutchinson Cancer Research Center and the Station
119 for Prevention and Treatment of Cancer in the STIB approved the study, in accordance with the
120 assurances of the Office for Human Research Protection of the US Department of Health and
121 Human Services. Informed consent was obtained prior to interview and blood draw.

122

123 **2.1.1 Case selection**

124

125 Case selection has been described in detail elsewhere [23, 25]. New cases of breast cancer (BC)
126 and benign breast disease were identified through review of factory medical clinic records and
127 visits to STIB hospitals. As described previously [25] 622 women with histologically confirmed
128 fibrocystic breast conditions (FBC) and 432 with BC were identified. For breast cancer cases

129 with adequate non-cancerous tissue (NCT) (at least 5 scanning power fields) from their biopsy,
130 the NCT was classified by one pathologist (ML) according to the scheme developed by Stalsberg
131 [26] as: nonproliferative (mild or no ductal hyperplasia and mild or no sclerosing adenosis),
132 proliferative without atypia (moderate or florid ductal hyperplasia or moderate or predominant
133 sclerosing adenosis and no atypia), or atypia (atypical ductal hyperplasia, atypical lobular
134 hyperplasia or moderate apocrine atypia). The lesions from women with FBC (and no breast
135 cancer) were similarly classified if adequate tissue was available.

136
137 As detailed elsewhere [27], in-person interviews were conducted primarily before histologic
138 diagnosis. Data collected during the interviews included demographics, medical history, and
139 known and suspected breast cancer risk factors (see [27] for more information). In our previous
140 study [23], women were excluded from analyses if blood was drawn >30 days prior to diagnosis
141 or >30 days from date of interview. For the present study, the time frame was expanded a priori
142 to include samples taken up to 90 days prior to diagnosis, given that most individuals maintain
143 producer/non-producer phenotypes over time and assignment of phenotypes is unlikely to be
144 influenced by timing of sampling. This resulted in the inclusion of two additional samples (taken
145 at 40 and 47 days prior to diagnosis). Samples drawn within 14 days after diagnosis were
146 included. Interviews were completed for 551 women with FBC (89%), and 443 of these (81%)
147 had plasma that was analyzed for equol (49 samples had been drawn after diagnosis). 302 (68%)
148 of these had histologic classifications as described. Interviews were completed for 378 (88%)
149 women with BC, and equol was measured in plasma from 269 (71%) women (23 samples had
150 been drawn after diagnosis). Of these, 191 (71%) had sufficient NCT for histologic classification.

151

152 **2.1.2 Control selection**

153

154 Control selection has been described in detail elsewhere [23, 25]. Controls were selected from
155 unaffected women in the BSE cohort and were frequency-matched to cases on age. Between
156 1995 and 1997 two controls per benign or malignant case (matched to case on age and menstrual
157 status) were recruited for a concurrent study of cell proliferation and were interviewed in their
158 home or factory (see [23, 25] for more detail). 367 of our controls were recruited in this way. For
159 cases enrolled between 1997 and 2000, controls were frequency matched by 5-year age group
160 and hospital affiliation of their factory in a 1:1 case-control ratio to the largest benign or
161 malignant case group in each age stratum. Interviews were completed in their homes or factories
162 for 704 (82%) of the 862 controls (see [23, 25] for more detail). One control whose calculated
163 daily energy intake was >4000 kcal was excluded. Of the 1070 eligible controls, 1027 had a
164 blood sample drawn at interview for analysis.

165

166 **2.2 Measurement of plasma isoflavones**

167

168 Plasma was frozen and stored at -70°C until assayed for equol using Labmaster time-resolved
169 fluoroimmunoassay (TR-FIA) kits (Turku, Finland). This method was used because it allowed
170 the inclusion of participants with small plasma volumes and provided for improved sensitivity
171 over other methods. Batches had similar distributions of cases and controls. Plasma (200 µl) was
172 incubated overnight at 37°C with 0.2 U/ml β-glucuronidase from E. Coli and 15 U/ml sulfatase
173 (Sigma-Aldrich Co., St. Louis, MO) in 200 µl 0.1 M acetate buffer pH 5. Hydrolyzed samples
174 were extracted twice, each with 1.5 ml ether. Ether fractions were dried under a stream of

175 nitrogen in a 37°C water bath, and the residue reconstituted in assay buffer. Samples were
176 vortexed, left for approximately 30 minutes, vortexed again and then used in the TR-FIA.
177 Fluorescence was measured on the Wallac Victor 2 model 1420 spectrofluorometer (Turku,
178 Finland). Data were analyzed using GraphPad Prism software (GraphPad Software Inc., San
179 Diego, CA). Samples with concentrations greater than the highest standard were assayed using a
180 new plasma aliquot, but the sample was diluted in assay buffer after reconstitution. We used an
181 estimated extraction recovery of 80% as per the package insert, and adjusted concentrations
182 accordingly. The inter-assay CV was 14.0%, and the limit of quantification (LOQ) was 0.66
183 nmol/L. Concentrations below this were reported as 0.33 nmol/L (i.e., half the LOQ), to allow
184 calculation of ratios.

185
186 Samples from most women had been analyzed for daidzein and genistein initially by liquid
187 chromatography-couarray method (LC-couarray; 32% of samples) and then by liquid
188 chromatography-mass spectrometry (LC-MS; 68% of samples); see [28] for further details on
189 these methods. As described previously [28], the analysis method was changed from LC-
190 couarray to LC-MS because increased instrument availability at the time meant that LC-MS
191 could be used, which improved assay efficiency and precision of the measurements. For 217
192 samples that had not already been analyzed, Labmaster TR-FIA kits (Turku, Finland) were used
193 to measure daidzein and genistein (64 samples for both daidzein and genistein; 49 for genistein
194 only; and 104 for daidzein only) because samples with small volumes could be measured with
195 improved sensitivity. Procedures were as described for equol. Daidzein concentrations <0.5
196 nmol/L were considered below LOQ and assigned the midpoint of 0.25 nmol/L. Genistein
197 concentrations <1.0 nmol/L were considered below LOQ and assigned the midpoint of 0.5

198 nmol/L. Inter-assay CVs were 9.1% for daidzein and 5.0% for genistein.

199

200 **2.3 Statistical Analyses**

201

202 The women had not received a soy challenge prior to blood sampling so a modified version of
203 the Setchell and Cole method [29] was applied to evaluate equol production in relation to risk of
204 FBC and BC. Setchell and Cole showed that serum equol >20 nmol/L distinguished equol
205 producers from non-producers, and the lowest serum daidzein concentration (following soy
206 exposure) was 16 nmol/L. Thus, we used two approaches to characterize equol exposure. First,
207 we grouped plasma equol into three categories (<20 , $20-<45$, and ≥ 45 nmol/L). Second, we
208 restricted analyses to women with plasma daidzein ≥ 20 nmol/L, calculated the ratio of equol to
209 daidzein (to allow for variation in soy intakes and pharmacokinetics/bioavailability), and \log_{10}
210 transformed the result, as per Setchell and Cole [29]. This yielded no clear separation of equol
211 producers from non-producers (data not shown), so we categorized the \log_{10} equol:daidzein ratio
212 into tertiles according to distributions among controls. Because we restricted these analyses to
213 women with plasma daidzein ≥ 20 nmol/L, additional categories (e.g., quintiles) would result in
214 very small numbers of cases per group. To enable comparisons with previous analyses [23], we
215 categorized daidzein and genistein concentrations into quartiles based on distributions among
216 controls. We used conditional logistic regression models to estimate odds ratios (OR) and 95%
217 confidence intervals (CI), and included strata for blood draw year (1995-1996, 1997, 1998-1999,
218 2000-2001) in all models to account for potential dietary changes prior to and during recruitment.
219 ORs were calculated across categories of equol, \log_{10} equol:daidzein ratio, daidzein, and
220 genistein. ORs for the \log_{10} equol:daidzein ratio in its continuous form were also estimated. We

221 computed the OR of FBC and BC by comparing each case group to the combined control group
222 (the matching of cases and controls from the first study was not retained in the analysis). We also
223 compared malignant and benign case groups to estimate risk of BC relative to FBC.

224

225 For women with histologic data, analyses were conducted according to proliferative status of the
226 NCT. Proliferative conditions with and without atypia were combined because the number of
227 women with atypia was small. Age (5-year categories), plasma genistein, and analysis method
228 for genistein were included in multiple logistic models for equol. Logistic models for log₁₀
229 equol:daidzein were adjusted for age and plasma daidzein analysis method. We evaluated
230 possible confounding effects of multiple factors, including age at first birth, number of live births,
231 total duration of lactation, years of oral contraceptive use, age at first menstrual period,
232 menopausal status, prior breast lump, times breast self-examination performed per year, body
233 mass index, and education as per our previous analysis [27]. None changed the results
234 appreciably (<10% change in the OR of the primary predictor variable) when added individually,
235 and were not included in final models. Tests for trend were performed by entering categorical
236 variables as continuous variables into regression models. All analyses were based on two-tailed
237 probability using SAS version 9.1 (SAS Institute Inc., Cary, NC).

238

239

240 **3. RESULTS**

241
242 Characteristics of BC cases, women with FBC, and controls were similar to those reported in our
243 previous studies of breast conditions in this population (Table 1) [23, 27, 30, 31].

244
245 Geometric mean plasma equol concentration among controls, women with FBC, and BC cases,
246 and also by age group are shown in Table 2. Among controls, equol concentrations ranged from
247 below the LOQ to 395 nmol/L, and 77.5% had concentrations <20 nmol/L (Figure 1). Among
248 BC cases, equol concentrations ranged from below the LOQ to 236 (82.9% had concentrations
249 <20 nmol/L) and among women with FBC equol concentration ranged from below the LOQ to
250 373 nmol/L (81.7% had concentrations <20 nmol/L).

251
252 We observed no associations of benign FBC, BC, or risk of BC vs. FBC in relation to categories
253 (i.e., <20, 20-<45, and \geq 45 nmol/L) of plasma equol concentration in all women or when
254 stratified by proliferative status of the FBC or NCT (Table 3). Associations of FBC and BC in
255 relation to tertiles of \log_{10} equol:daidzein ratio in women with plasma daidzein concentrations
256 \geq 20 nmol/L are shown in Table 4. Proliferative FBC, BC with proliferative NCT (including
257 atypia), and all BC combined (i.e., all women with and without histological classification) were
258 positively associated with the second tertile of \log_{10} equol:daidzein ratio, but trends across
259 tertiles were not observed. Furthermore, no linear trends were observed when considering the
260 ratio as a continuous variable. Findings did not change substantially when restricting analyses to
261 people whose blood sample was drawn at or before diagnosis, although the OR for proliferative
262 FBC for the second tertile of the \log_{10} equol:daidzein ratio was attenuated (OR 1.80, 95% CI

263 0.92-3.51). Similarly, findings did not change substantially when restricting analyses to cases
264 and controls with daidzein measured by LC-MS, although the ORs (95% CI) for FBC vs.
265 controls for non-proliferative conditions were 0.38 (0.11-1.32) and 0.20 (0.04-1.01) for the
266 second and third tertiles of the \log_{10} equol:daidzein ratio, respectively (p trend 0.04), and
267 proliferative FBC, BC with proliferative NCT, and BC combined (i.e., all women with and
268 without histological classification) were no longer positively associated with the second tertile of
269 the \log_{10} equol:daidzein ratio. However, these findings were based on small numbers of cases.

270

271 For risks of FBC and BC in relation to plasma daidzein and genistein, our findings were similar
272 to those reported previously among the slightly smaller sample [23], although findings for
273 genistein in relation to proliferative FBC were attenuated; briefly, the ORs (95% CI) for the
274 highest quartiles (compared to lowest) of daidzein and genistein, respectively, were 0.17 (0.08-
275 0.38) and 0.30 (0.15-0.60) for non-proliferative FBC and 0.32 (0.15-0.67) and 0.55 (0.29-1.08)
276 for proliferative FBC. The corresponding ORs (95% CI) were 0.26 (0.11-0.62) and 0.43 (0.20-
277 0.96) for BC with concurrent non-proliferative NCT and 0.27 (0.11-0.67) and 0.22 (0.08-0.57)
278 for BC with concurrent proliferative NCT.

279

280

281 **4. DISCUSSION**

282

283 In this population-based case-control study, no trends in risks of either BC or FBC (with or
284 without proliferative changes), were observed with increasing or decreasing levels of either
285 plasma equol concentration or the \log_{10} equol:daidzein ratio. Positive associations were seen for
286 women in the mid tertile of the \log_{10} equol:daidzein ratio for proliferative FBC, BC with
287 proliferative NCT, and total BC. However, the absence of a trend across tertiles and no linear
288 trend when considered in its continuous form suggests that these observations do not represent a
289 biological phenomenon. We reject our hypothesis of an inverse association between plasma
290 equol and risks of FBC and BC among women in Shanghai, China. The inverse association
291 previously shown between plasma daidzein and genistein and risk of these breast conditions [23]
292 remained with the larger sample size, although findings were slightly attenuated.

293

294 The effects of equol on human health have been examined previously using blood and urine
295 concentrations of equol or dichotomizing on ability to produce equol [10]. To measure equol,
296 individuals must be exposed to sufficient daidzein prior to sampling. However, as noted by
297 Setchell and Cole [29], there have been inconsistencies across studies in, for example, the
298 amounts of soy/daidzein consumed and cut points for assigning equol-producer status. Although
299 we did not see a clear demarcation between equol producers and non-producers using plasma
300 concentrations, we accounted for this in our analyses by applying some of the criteria specified
301 by Setchell and Cole [29]. Despite this, we did not see any consistent associations between equol
302 production and risks of BC or FBC.

303

304 Our findings are in agreement with Virk-Baker et al. who reported no associations between
305 equol-producer status (assessed using a soy challenge) and breast pathology, hyperplasia, or
306 breast cancer among US women who had undergone breast biopsies following an abnormal
307 mammogram [32]. In relation to potential modifying effects of equol production on other breast
308 cancer risk factors, there have been suggestions of greater effects of isoflavone supplementation
309 in equol-producers in relation to estrogen-responsive genes [33], or interactions between equol-
310 producer phenotype and soy intake in relation to mammographic density [19, 20]. However, a
311 soy protein intervention study did not show equol-producer status as an effect modifier regarding
312 mammographic density [34] and there was no effect of equol production on urinary estrogen
313 metabolites in soy supplementation studies [35].

314

315 It is possible that the lack of associations in this study may have been due to limited numbers of
316 equol-producers or low circulating concentrations. Around 20% of the women had plasma equol
317 concentrations ≥ 20 nmol/L which is on the lower end of reported proportions of equol-producers
318 [10]. Furthermore, although equol concentration in our study was higher than or similar to
319 plasma concentrations among men and women in studies of different cancer types in the US or
320 Europe [13, 15, 36, 37], it was lower than concentrations in some studies in Japanese and Korean
321 populations [38-40].

322

323 Our study has several strengths. It is a large population-based study in women who typically
324 consume soy foods [28], and most blood samples were drawn before diagnosis or treatment.
325 However, blood was drawn from cases at the time of biopsy and women could have modified
326 their diet prior to the hospital visit. Although this could potentially affect overall circulating

327 isoflavone concentrations, it is unlikely to affect the capacity of gut microbes to metabolize
328 daidzein to equol. In addition, since most of the cases were asymptomatic and biopsies are
329 considered a minor out-patient procedure, it is unlikely that the women altered their diets as a
330 result of their condition. Also, the women were not instructed to make any changes to their
331 habitual activities or diet in preparation for the hospital visit. Another strength of this study is
332 that the available tissue for histological classification was reviewed by one study pathologist.

333
334 One limitation of our study is that we did not administer a soy challenge to classify women
335 according to their equol-producing status. As such, we may have misclassified some individuals
336 due to inadequate or inconsistent soy exposure. Since this misclassification would likely have
337 been the same in cases and controls, this would have the effect of underestimating any true
338 relationship, and could be an explanation for the absence of associations in this study. In a
339 previous study of Chinese men and women consuming their usual diet, the number of equol
340 producers more than doubled when a soy challenge was administered, suggesting that even in
341 populations with high habitual levels of soy consumption the number of equol-producers may be
342 underestimated [41]. Furthermore, in our study, equol was assessed at only one time point.
343 Although equol production has been shown to be relatively stable within individuals over time in
344 some studies [42, 43], others have suggested that around 6 to 20% of individuals vary or
345 crossover equol phenotypes over relatively short periods of time [44, 45]. However, the evidence
346 to date suggests there is more often a producer to non-producer shift than vice versa [42-45]. If
347 that is the case, it may be more likely that non-producers rather than producers were
348 misclassified. Another limitation of this study is that plasma equol concentrations reflect short-
349 term intake and may not reflect exposure at the relevant time for the development of proliferative

350 mammary epithelial changes, or of cancer initiation or progression. In addition, there may have
351 been insufficient statistical power to evaluate associations, especially for analyses including
352 strata with few cases. Also, different methods of isoflavone analysis were used and daidzein
353 concentrations were slightly lower with LC-MS [28]. However, samples from both cases and
354 controls were measured by LC-MS and it is unlikely that any systematic differences were
355 introduced. Nonetheless, we adjusted for isoflavone analysis method in our statistical model, and
356 when restricting analyses to samples measured by LC-MS, findings did not change substantially.
357 Finally, our study was largely restricted to Han Chinese women residing in one industrial city in
358 China, and the results may not be applicable to women of other races or to women living in
359 different social or physical conditions.

360

361 In conclusion, the results of this study do not provide evidence that equol plays a role in the
362 etiology of FBC or breast cancer. However, future studies are needed to more fully explore the
363 potential effects of equol production on risks of these breast conditions.

364

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366

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377

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379

380 **6. REFERENCES**

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Table 1. Selected characteristics of controls, women with fibrocystic breast conditions and breast cancer cases ^a

	Controls	Fibrocystic Breast Conditions			Breast Cancer Cases		
	n=1027	Non-proliferative n=130 ^b	Proliferative n=172 ^b	All n=443 ^b	Non-proliferative NCT ^c n=99 ^b	Proliferative NCT n=92 ^b	All n=269 ^b
Age (years)							
≤ 39	13 (1.3)	17 (13.1)	16 (9.3)	57 (12.9)	3 (3.0)	4 (4.3)	9 (3.3)
40-44	457 (44.5)	54 (41.5)	81 (47.1)	198 (44.7)	27 (27.3)	24 (26.1)	75 (27.9)
45-49	215 (20.9)	33 (25.4)	46 (26.7)	117 (26.4)	19 (19.2)	25 (27.2)	56 (20.8)
50-59	121 (11.8)	14 (10.8)	9 (5.2)	28 (6.3)	21 (21.2)	11 (12.0)	40 (14.9)
≥ 60	221 (21.5)	12 (9.2)	20 (11.6)	43 (9.7)	29 (29.3)	28 (30.4)	89 (33.1)
Number of live births							
None	37 (3.6)	7 (4.9)	8 (3.8)	20 (3.7)	6 (5.9)	6 (6.2)	16 (5.2)
1	694 (67.8)	95 (62.5)	137 (68.5)	350 (66.4)	49 (63.4)	57 (70.8)	145 (66.8)
2	119 (11.6)	12 (9.4)	12 (12.0)	30 (10.5)	23 (15.5)	9 (7.4)	44 (12.3)
≥ 3	173 (16.9)	14 (23.2)	15 (15.8)	40 (19.3)	21 (15.2)	20 (15.7)	64 (15.7)

Age at first live birth (years)

≤ 24	258 (26.3)	23 (26.3)	29 (25.8)	68 (25.9)	30 (24.5)	26 (24.0)	84 (25.0)
25-29	582 (58.9)	79 (60.2)	106 (59.9)	283 (60.5)	43 (52.9)	40 (51.3)	120 (54.2)
≥ 30	146 (14.8)	19 (13.5)	29 (14.3)	68 (13.6)	18 (22.6)	20 (24.7)	47 (20.8)

Months of breast feeding

Never	174 (17.7)	20 (17.1)	33 (16.8)	83 (18.1)	14 (16.8)	16 (21.4)	38 (17.3)
≤ 6	203 (20.7)	30 (24.2)	50 (29.2)	118 (26.1)	20 (24.4)	16 (18.2)	50 (21.5)
7-12	352 (36.0)	44 (28.5)	50 (28.3)	146 (29.6)	26 (32.5)	30 (39.9)	83 (38.0)
13-24	110 (11.3)	13 (14.0)	12 (10.5)	31 (11.0)	18 (15.3)	6 (5.5)	33 (10.5)
≥ 25	139 (14.3)	10 (16.2)	15 (15.2)	139 (14.3)	14 (11.0)	18 (15.0)	48 (12.8)

Duration of oral contraceptive use

Never used	939 (91.5)	110 (83.4)	155 (88.1)	395 (87.1)	87 (86.9)	80 (87.6)	240 (89.8)
≤ 1 year	34 (3.3)	10 (9.3)	8 (4.2)	26 (6.5)	8 (8.7)	7 (8.0)	16 (6.2)
> 1 year	53 (5.2)	10 (7.3)	9 (7.7)	21 (6.5)	4 (4.4)	5 (4.4)	13 (4.0)

Age at first menstrual period (years)

≤ 13	163 (15.9)	28 (16.7)	25 (14.0)	84 (16.7)	24 (28.1)	15 (13.4)	53 (21.7)
14	200 (19.5)	29 (23.1)	44 (22.5)	101 (21.4)	16 (19.5)	17 (21.7)	53 (22.3)
15	204 (19.9)	26 (20.4)	35 (19.8)	96 (21.1)	24 (21.7)	20 (23.5)	62 (22.1)
16	213 (20.8)	22 (14.0)	32 (19.2)	73 (16.3)	17 (17.0)	15 (13.8)	44 (14.8)
≥ 17	246 (24.0)	25 (25.8)	36 (24.4)	88 (24.6)	18 (13.7)	25 (27.6)	57 (19.1)

Menopause

Yes	357 (34.8)	25 (32.0)	37 (34.0)	80 (32.9)	50 (36.5)	39 (32.4)	127 (33.7)
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Prior breast lumps

Yes	31 (3.1)	10 (6.7)	24 (13.5)	48 (9.8)	5 (6.3)	8 (8.6)	16 (7.2)
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Times breast self-examination per year

Never	697 (68.1)	47 (41.1)	70 (44.3)	169 (41.6)	51 (51.0)	51 (51.0)	140 (49.6)
1-6	135 (13.2)	21 (11.4)	26 (12.6)	73 (14.0)	17 (19.9)	18 (19.4)	55 (21.5)
7-12	186 (18.2)	59 (45.2)	70 (40.0)	185 (41.2)	29 (27.7)	22 (27.8)	68 (26.9)
≥ 13	6 (0.6)	3 (2.3)	6 (3.1)	14 (3.2)	2 (1.5)	1 (1.9)	5 (2.0)

Education

Elementary school or less	193 (18.9)	11 (17.6)	14 (14.2)	35 (16.3)	30 (21.7)	20 (15.7)	79 (19.8)
Middle school	803 (78.2)	110 (75.5)	149 (80.0)	384 (77.9)	63 (74.6)	64 (76.5)	172 (74.7)
College	30 (2.9)	9 (6.9)	9 (5.8)	23 (5.7)	6 (3.7)	8 (7.8)	18 (5.5)
Body mass index (kg/m²)							
≤ 20	192 (18.7)	39 (26.0)	36 (16.0)	116 (21.2)	16 (18.0)	17 (18.4)	43 (16.3)
21-25	603 (58.7)	72 (56.5)	101 (58.8)	253 (57.1)	61 (62.0)	50 (56.9)	158 (61.2)
> 25	232 (22.6)	19 (17.5)	35 (25.2)	73 (21.6)	22 (20.0)	25 (24.7)	68 (22.5)

^a Data are shown as n (%); total numbers per variable may not add up to the total number of women per column due to some missing data

^b Indirect age-adjusted percentages based on age distribution of the controls

^c NCT = non-cancerous tissue

Table 2. Plasma equol concentration among controls, women with fibrocystic breast conditions (FBC) and breast cancer (BC) cases by age group

	Controls		FBC cases		BC cases	
	n	Geometric mean (95% CI) ^a	n	Geometric mean (95% CI) ^a	n	Geometric mean (95% CI) ^a
	All ages combined	1027	6.87 (6.25, 7.55)	443	5.45 (4.76, 6.24)	269
Age ≤39	13	7.83 (3.16, 19.40)	57	5.02 (3.27, 7.71)	9	2.88 (0.88, 9.44)
Age 40-44	457	6.81 (5.90, 7.85)	198	5.31 (4.33, 6.50)	75	6.41 (4.67, 8.79)
Age 45-49	215	5.79 (4.75, 7.06)	117	5.71 (4.42, 7.38)	56	4.68 (3.28, 6.67)
Age 50-59	121	6.39 (5.02, 8.14)	28	4.02 (2.52, 6.41)	40	4.65 (3.08, 7.02)
Age ≥60	221	8.53 (6.89, 10.6)	43	7.41 (4.92, 11.2)	89	6.46 (4.85, 8.59)

^a data presented as geometric mean and 95% confidence interval; plasma equol concentration in nmol/L

Table 3. Fibrocystic breast conditions (FBC) and breast cancer in relation to plasma equol concentrations

	Number of women (%)			FBCs vs. controls		Breast cancer vs. controls		Breast cancer vs. FBCs	
	Control	FBC	Cancer	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI
Equol (nmol/L)									
Non-proliferative NCT^b									
< 20	796 (77.5)	107 (82.3)	86 (86.9)	1.00	Ref.	1.00	Ref.	1.00	Ref.
20 to <45	114 (11.1)	13 (10.0)	6 (6.1)	1.27	0.59-2.74	0.67	0.26-1.74	0.69	0.24-2.03
≥45	117 (11.4)	10 (7.7)	7 (7.1)	1.25	0.54-2.90	0.93	0.36-2.40	0.80	0.26-2.49
p trend					0.49		0.64		0.53
Proliferative NCT (including atypia)									
< 20	796 (77.5)	143 (83.1)	74 (80.4)	1.00	Ref.	1.00	Ref.	1.00	Ref.
20 to <45	114 (11.1)	18 (10.5)	9 (9.8)	1.09	0.51-2.32	0.94	0.38-2.32	1.28	0.51-3.20
≥45	117 (11.4)	11 (6.4)	9 (9.8)	0.70	0.28-1.74	1.88	0.75-4.70	1.73	0.59-5.06
p trend					0.57		0.26		0.28

Total									
< 20	796 (77.5)	362 (81.7)	223 (82.9)	1.00	Ref.	1.00	Ref.	1.00	Ref.
20 to <45	114 (11.1)	48 (10.8)	27 (10.0)	1.05	0.61-1.80	1.06	0.59-1.83	0.97	0.56-1.67
≥45	117 (11.4)	33 (7.4)	19 (7.1)	0.84	0.46-1.53	1.18	0.61-2.29	0.91	0.47-1.74
p trend					0.64		0.61		0.76

^a Data are presented as odds ratios (ORs) and 95% confidence intervals (CIs); ORs were adjusted for age, plasma genistein (quartiles), and lab method for genistein analysis, and included a strata variable for blood draw year

^b NCT = non-cancerous tissue

Table 4. Fibrocystic breast conditions (FBC) and breast cancer in relation to log₁₀ plasma equol:daidzein ratio among women with plasma daidzein concentration ≥20 nmol/L

	Number of women (%)			FBCs vs. controls		Breast cancer vs. controls		Breast cancer vs. FBCs	
	Control	FBC	Cancer	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI
	Log₁₀ plasma equol:daidzein ratio								
Non-proliferative NCT^b									
-3.35 to -1.43	258 (33.3)	20 (29.0)	19 (30.6)	1.00	Ref.	1.00	Ref.	1.00	Ref.
-1.42 to -0.77	258 (33.3)	24 (34.8)	28 (45.2)	1.02	0.48-2.13	1.76	0.89-3.47	1.36	0.83-6.71
-0.76 to 1.96	258 (33.3)	25 (36.2)	15 (24.2)	1.14	0.54-2.39	0.87	0.40-1.88	1.09	0.36-3.28
p trend					0.37		0.48		0.40
Continuous log ₁₀ plasma equol:daidzein ratio				1.21	0.79-1.84	0.91	0.60-1.37	0.78	0.42-1.46
p-value					0.38		0.66		0.44

Proliferative NCT (including atypia)

-3.35 to -1.43	258 (33.3)	27 (26.5)	13 (20.3)	1.00	Ref.	1.00	Ref.	1.00	Ref.
-1.42 to -0.77	258 (33.3)	48 (47.1)	35 (54.7)	2.06	1.08-3.93	2.95	1.37-6.35	1.37	0.59-3.22
-0.76 to 1.96	258 (33.3)	27 (26.5)	16 (25.0)	1.05	0.51-2.16	1.36	0.58-3.23	1.36	0.51-3.67
p trend					0.81		0.31		0.31

Continuous log ₁₀ plasma equol:daidzein ratio				1.13	0.76-1.68	1.38	0.88-2.15	1.37	0.77-2.42
p-value					0.56		0.16		0.28

Total

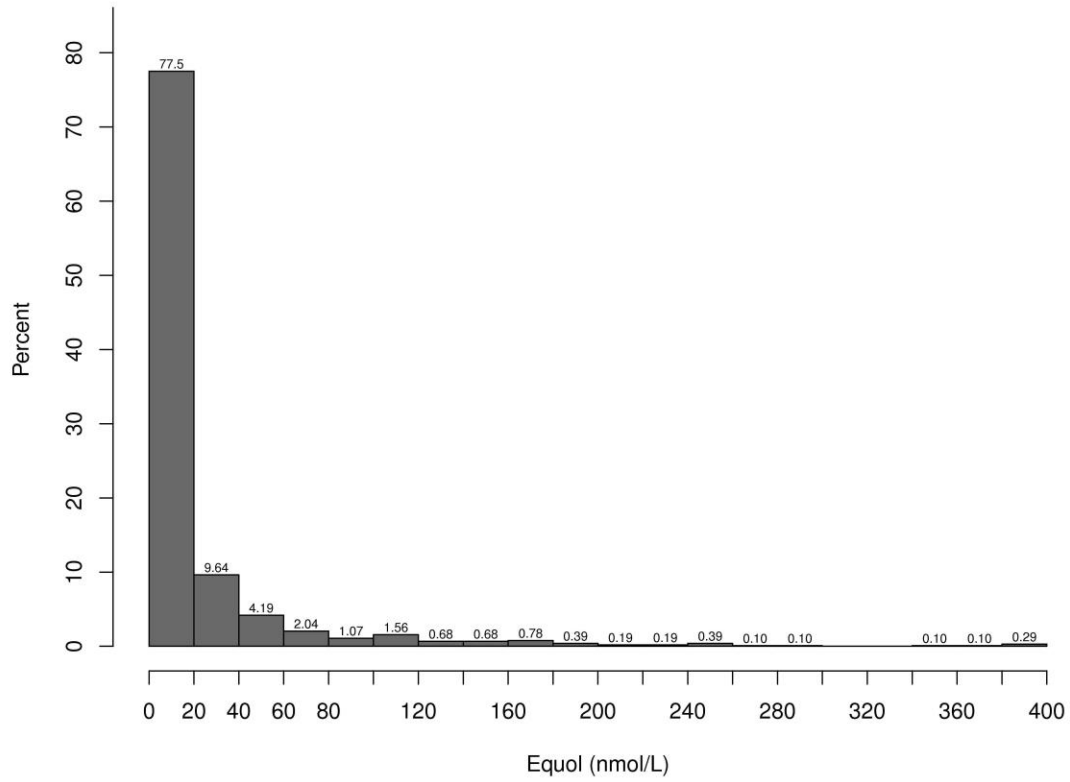
-3.35 to -1.43	258 (33.3)	78 (27.8)	45 (25.6)	1.00	Ref.	1.00	Ref.	1.00	Ref.
-1.42 to -0.77	258 (33.3)	115 (40.9)	82 (46.6)	1.57	0.99-2.51	2.37	1.43-3.95	1.44	0.85-2.43
-0.76 to 1.96	258 (33.3)	88 (31.3)	49 (27.8)	1.17	0.71-1.93	1.26	0.72-2.18	1.10	0.62-1.94
p trend					0.42		0.38		0.92

Continuous log ₁₀ plasma equol:daidzein ratio				1.19	0.90-1.58	1.20	0.89-1.62	0.95	0.69-1.33
p-value					0.23		0.24		0.78

^a Data are presented as odds ratios (ORs) and 95% confidence intervals (CIs); ORs were adjusted for age and lab method for daidzein analysis, and included a strata variable for blood draw year

^b NCT = non-cancerous tissue

Figure 1. Frequency distribution of plasma equol concentration among control women ^a



^a n=1027