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EPIDEMIOLOGY

Severe acne and risk of breast cancer

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Abstract

Purpose Hormonal imbalance early in life is thought to be associated with breast cancer risk. Severe acne may arise from hormonal imbalance and could serve as an indicator of increased breast cancer risk. We explored whether severe acne was associated with incident breast cancer.

Methods We used data from the Sister Study, a large ($n = 50{,}884$) prospective cohort of women who had a sister diagnosed with breast cancer, but who were free of breast cancer themselves at baseline. Participants completed a structured questionnaire that included demographics, lifestyle factors, and medical history, including any diagnosis of severe acne. Adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association of severe acne and breast cancer (invasive disease or ductal carcinoma in situ).

Results During an average of 8.4 years of follow-up, 3049 breast cancer cases were diagnosed. Ever being diagnosed with severe acne was associated with a higher risk of breast cancer (HR 1.23; 95% CI 0.98, 1.54), particularly in women who were diagnosed prior to age 18 years (HR 1.40; 95% CI 1.04, 1.90). Results were similar when limited to invasive cancers.

Conclusions Our study supports a non-significant positive association between severe acne—a potential marker of hormonal imbalance—and breast cancer risk. These findings suggest that severe acne, when considered along with other risk factors, could help to identify women who may be at a higher risk of breast cancer.

Keywords Severe acne · Epidemiology · Hormones · Risk factors

Introduction

Breast cancer is typically diagnosed among older women, with a median age at diagnosis of 62 years in the United States [1]. However, some important risk factors for the disease occur during early life, including birth size, age at menarche, adolescent adiposity, adolescent exposure to tobacco smoke, and physical activity before first pregnancy [2–9]. Evidence suggests that these risk factors may alter circulating hormone levels [10]. Higher endogenous estrogen and androgen levels have been positively associated with breast cancer in postmenopausal women [11–16]. High androgen level-related conditions such as polycystic ovarian syndrome (PCOS) have also been associated with incident breast cancer [17].

Higher circulating androgen levels are also associated with acne [18], an extremely common skin condition affecting more than 85% of individuals aged 12–25 and frequently continuing into adulthood [19]. Indeed, 26% of women and 12% of men in their forties report having acne [20]. Higher androgen levels over-stimulate the sebaceous glands and alter the development of skin cells lining hair follicles. Although most acne cases resolve by themselves, about 40% of individuals require clinical treatment for acne during early adulthood [21]. Such "severe acne" is usually treated with isotretinoin (former brand name: Accutane) or systemic antibiotics [22].

Given that higher circulating estrogen and androgen levels are positively associated with both severe acne and breast cancer, history of severe acne (e.g., cystic or scarring acne) could be predictive of breast cancer risk. A recent study by Zhang et al., using data from the Nurses' Health Study II, reported a 17% higher risk of breast cancer in association

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with severe teenage acne [23]. Our study seeks to further elucidate the association between severe acne and breast cancer risk by replicating and expanding on Zhang et al.'s study using data from the Sister Study, a large cohort of women in the United States. Sister Study participants self-reported severe acne at any time in their life. Therefore, we were able to evaluate the importance of timing of acne on breast cancer risk. Additionally, we collected information on common acne treatments, which we hypothesized could affect the acne-breast cancer association or function to identify the most severe cases of acne.

Methods

Study sample

The Sister Study is a prospective cohort of 50,884 women ages 35–74, recruited between 2003–2009 in the United States and Puerto Rico [24]. Women were eligible if they had never been diagnosed with breast cancer but had at least one sister who had been diagnosed with breast cancer. Baseline data collection consisted of computer-assisted telephone interviews, self-completed questionnaires, and in-home examiner visits. Follow-up is ongoing, collecting basic health data annually and more detailed data every 2–3 years. Data for this analysis are complete through September 2016 (data release 6.0). More than 90% of participants have responded to the latest follow-up questionnaire. The study was reviewed and approved by the Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus group [24]. All participants provided written informed consent.

We excluded women who developed breast cancer before baseline, had an uncertain history of breast cancer or unknown age at diagnosis ($n=74$), or withdrew their consent ($n=2$). Our final analysis dataset consisted of 50,808 women. Among these, 3056 women were diagnosed with invasive breast cancer or ductal carcinoma in situ (DCIS) during follow-up.

The primary exposure variable—severe acne diagnosis—was determined from this baseline question: "Has a doctor or other health professional ever told you that you had severe or cystic scarring acne?" Participants who answered "yes" to this question were considered exposed.

Participants who reported severe acne were asked about their age at diagnosis. To evaluate the importance of timing of severe acne exposure, we considered whether women were exposed prior to age 18 years (the median age at severe acne diagnosis) or, separately, before their first pregnancy. To further assess the impact of severe acne in early life, we examined self-reported personal blemish or acne products use at ages 10–13 years ("did not use," "sometimes," "frequently," and, "don't know."). Additionally, we considered participants who were diagnosed with severe acne in addition to having frequently used blemish/acne products ages 10–13. We refer to this final exposure variable as "severe and adolescent acne."

We additionally considered two alternative exposures for treated acne: (1) Accutane and (2) acne-specific antibiotic use. Under these two exposure definitions, participants were considered exposed if they reported ever taking Accutane or, separately, antibiotics to treat their acne. Participants reported their reason for using antibiotics on the baseline questionnaire; those who reported the reason as "acne" or similar were considered exposed under this definition.

Women who reported incident breast cancer diagnosis during follow-up were asked to allow their medical records to be released [25]. We were able to obtain medical records for 82% of incident breast cancer cases [26]. Agreement between self-reported and medical record data was high (99%); therefore, self-reported data were used when medical record data were missing [26].

Statistical analysis

We used Cox proportional hazards regression to model the association between severe acne and breast cancer, using age as the time scale. Women were followed from age at study enrollment to age at breast cancer diagnosis, with censoring at death, loss to follow-up, or September 15, 2016. Because some families included more than one sister in the study, we used robust variance estimators to account for correlations between sisters due to shared genetic and environmental factors. The proportionality assumption was tested using Wald χ^2 tests at the 95% confidence level of interaction terms between the exposure of interest and time.

Due to the timing of the questionnaire, it was difficult to establish whether several confounders preceded severe acne diagnosis. Therefore, two adjustment models were considered: one minimally-adjusted and one fully-adjusted. The minimally-adjusted model only included race/ethnicity (non-Hispanic White, African-American, Hispanic, other), and the participant's head of household's highest educational attainment when the participant was 13 years old (a marker for socioeconomic status; high school or less, some college, bachelor's degree, graduate degree). In the fully-adjusted model, the HR was adjusted for: age at menarche, age at first birth (as an interaction term with ever/never parity), body mass index (BMI; a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles), menopausal status at baseline (pre or postmenopausal), history of hormonal contraceptive use (never used, last used within 5 years, used more than 5 years prior), history of hormone replacement therapy (never, estrogen alone, estrogen plus progestin), parity (nulliparous, 1, 2, ≥ 3 births), smoking status (never,

former, current), and alcohol use (never/former, current < 1 drink/day, current ≥ 1 drink/day), in addition to race/ethnicity and participant's baseline educational attainment. An interaction term between BMI and menopausal status was also included, because BMI is associated differently with pre- versus postmenopausal breast cancer [25, 27]. To test for a trend in the personal acne/blemish product use variable, we calculated the association p value for the ordinal form of the variable.

To assess effect measure modification, we examined the association between severe acne and breast cancer risk within strata of race/ethnicity, parity (nulliparous vs. parous), BMI (< 30 kg/m^2 vs. ≥ 30 kg/m^2), hormone therapy use, oral contraceptive use, age at menarche (≤ 12 years vs. > 12 years), and family history of breast cancer (1 sister/half-sister vs. ≥ 2 first-degree relatives). We also examined modification by menopausal status updated over follow-up. We tested for HR heterogeneity using likelihood ratio tests of the interaction between severe acne and each modifier.

We conducted various sensitivity analyses, including adjusting for oophorectomy status at baseline (both ovaries removed vs. one or neither removed), excluding women who had PCOS, adjusting for use of acne/blemish product use at ages 10–13 (frequent vs. infrequent or never), and excluding women who had had prophylactic mastectomy before baseline (Supplementary Table 2). We repeated these sensitivity analyses when estimating the effect of severe and adolescent acne. We additionally examined the association between acne and specific types of cancer (invasive, DCIS, estrogen receptor [ER] +, and ER −), including case–case comparisons. For these analyses, we censored other breast cancers at their age of diagnosis.

Results

1098 participants (2%) reported a severe acne diagnosis (Table 1). Mean overall follow-up time was 8.4 years. The Sister Study cohort is predominantly non-Hispanic White (84% of unexposed) and highly educated (85% of unexposed had at least some college). Exposed women were more likely to be premenopausal than unexposed women (45% vs. 34%), to have been diagnosed with PCOS (5% vs. 2%), to have used hormonal contraception within the past 5 years (14% vs. 9%), to have had their first pregnancy after age 30 (17% vs. 12%), and to be nulliparous (24% vs. 18%). Differences in covariate distribution by breast cancer case status are reported in Supplementary Table 1.

Among participants with complete data on all potential confounders, two percent (n = 1081) reported a diagnosis of severe acne (Table 2). Fourteen percent (n = 6756) had frequently used acne/blemish products at ages 10–13. Among participants with severe acne, 47% (n = 507) were diagnosed before age 18. One percent of all participants (n = 459) reported both severe acne diagnosis and use of acne/blemish products at ages 10–13.

Regression model results were similar comparing minimally with fully-adjusted models (Table 2). For all exposures, Wald χ^2 tests of age by acne interaction terms supported proportionality of hazard functions. In the fully-adjusted models, we observed a statistically non-significant positive association between breast cancer and severe acne diagnosis (HR 1.23; 95% CI 0.98, 1.54). Results were stronger for diagnosis of severe acne before age 18 (HR 1.40; 95% CI 1.04, 1.90) versus age 18 or later (HR 1.08, 95% CI 0.77, 1.51; p for heterogeneity = 0.25). Results were similar between those diagnosed with acne before their first pregnancy versus after. We observed only a modest increase in risk for frequent acne/blemish product use at ages 10–13 (HR 1.07; 95% CI 0.96, 1.23; p for trend = 0.25). However, when we considered those who reported both severe acne and frequent adolescent acne product use, relative to everyone else, we observed a higher breast cancer risk (HR 1.35; 95% CI 0.97, 1.87).

When we considered treated acne, we observed a near-null association between Accutane use and breast cancer (HR 1.07, 95% CI 0.84, 1.35). However, risk was higher among women who had ever used Accutane for acne or had been diagnosed with severe acne (HR 1.17; 95% CI 0.98, 1.39). Similarly, women who reported ever using systemic antibiotics for acne treatment were more likely to develop breast cancer than women who did not (HR 1.17; 95% CI 1.00, 1.35).

Stratified analyses were consistent with main findings (Table 3), and none of the interaction terms was significant. Sensitivity analyses were also consistent with main findings (Supplementary Table 2). Results largely did not differ by breast cancer case definition (Table 4). However, all associations were stronger among women diagnosed with severe acne before age 18, relative to those with no severe acne.

Discussion

In this large, prospective study we observed a statistically non-significant positive association between breast cancer and severe acne diagnosis, particularly among women who experienced severe acne during adolescence. These results are consistent with the hypothesis that early-life hormone levels may influence breast cancer risk. Elevated sex hormones have previously been associated with both severe acne and increased breast cancer risk [11–13, 18].

Our effect estimates were similar to those reported by Zhang et al. for severe teenage acne (HR 1.17; 95% CI 1.03, 1.32) [23]. We expanded on Zhang et al.'s study by examining severe acne exposure at all ages. The Sister

Table 1 Baseline characteristics of the Sister Study cohort (2003–2009)[a] by exposure status

	No severe acne diagnosis ($N=49{,}669$)	Severe acne diagnosis ($N=1098$)
Age in years; mean (std[b])	55.7 (9.0)	53.2 (8.7)
Follow-up time in years; mean (std[b])	8.4 (2.2)	8.4 (2.1)
Age at menarche in years; mean (std[b])	12.6 (1.5)	12.5 (1.5)
Race; *N* (%)		
Non-Hispanic White	41,495 (84)	966 (88)
Non-Hispanic Black	4,395 (9)	58 (5)
Hispanic	2457 (5)	53 (5)
Other	1307 (3)	21 (2)
Participant's highest education level; *N* (%)		
High school or less	7685 (15)	101 (9)
Some college	16,816 (34)	332 (30)
Bachelor's degree	13,348 (27)	334 (30)
Graduate degree	11,808 (24)	331 (30)
Head of household's highest education level when participant was 13 years old; *N* (%)		
High school or less	26,729 (54)	516 (47)
Some college	9262 (19)	215 (20)
Bachelor's degree	7978 (16)	221 (20)
Graduate degree	5110 (10)	139 (13)
Body mass index (BMI); *N* (%) (kg/m^2)		
<25.0	18,923 (38)	469 (43)
25–29.9	15,763 (32)	346 (32)
≥ 30	14,966 (30)	283 (26)
Baseline menopausal status; *N* (%)		
Premenopausal	16,981 (34)	489 (45)
Postmenopausal	32,688 (66)	609 (55)
Polycystic ovarian syndrome (PCOS); *N* (%)		
Never diagnosed	48,349 (98)	1040 (95)
Ever diagnosed	1222 (2)	56 (5)
Hormonal contraception: how recently used; *N* (%)		
Never	7348 (15)	115 (11)
≥ 5 years ago	37,400 (76)	831 (76)
<5 years ago	4645 (9)	148 (14)
Hormone therapy use; *N* (%)		
None	28,423 (57)	694 (64)
Estrogen alone	9848 (20)	187 (17)
Estrogen plus progestin	11,263 (23)	210 (19)
Age at first pregnancy; *N* (%)		
No pregnancies	6182 (12)	172 (16)
<20 years	9482 (19)	162 (15)
20–24.9 years	17,319 (35)	313 (29)
25–29.9 years	10,649 (21)	261 (24)
≥ 30 years	5948 (12)	187 (17)
Parity; *N* (%)		
No births	8919 (18)	266 (24)
1 birth	7169 (14)	167 (15)
2 births	18,228 (37)	416 (38)
≥ 3 births	15,322 (31)	247 (23)
Smoking status; *N* (%)		

Table 1 (continued)

	No severe acne diagnosis ($N=49,669$)	Severe acne diagnosis ($N=1098$)
Never	27,876 (56)	612 (56)
Former	17,705 (36)	394 (36)
Current	4072 (8)	92 (8)
Alcohol use; *N* (%)		
Never or former	9460 (19)	194 (18)
Current, < 1 drink/day	33,420 (67)	761 (70)
Current ≥ 1 drink/day	6705 (14)	140 (13)
Family history of breast cancer		
1 affected sister or half-sister	36,455 (73)	814 (74)
≥ 2 affected 1st degree relatives	13,213 (27)	284 (26)

Missing values: age at menarche (45 exposed), race (15 unexposed), education at baseline (12 unexposed), head of household's education when participant was 13 years old (590 unexposed, 7 exposed), BMI (17 unexposed), PCOS (98 unexposed, 2 exposed), hormonal contraception use (276 unexposed, 4 exposed), hormone therapy use (135 unexposed, 7 exposed), age at first pregnancy (89 unexposed, 3 exposed), parity (31 unexposed, 2 exposed), smoking (16 unexposed), alcohol use (84 unexposed, 3 exposed), 1st degree family history of breast cancer (1 unexposed)

[a]Excludes women withdrawn from the study ($N=2$), women who were diagnosed with breast cancer before completion of the baseline interview or had an uncertain diagnosis or an unknown age at diagnosis ($N=8174$). 41 women were missing data for severe acne diagnosis

[b]Standard deviation

Study was well-suited to address this research question because, by recruiting women who all had a family history of breast cancer, it enriched the study population at risk for breast cancer, thus making breast cancer risk factor research more efficient [28].

We also explored the impact of acne treatments on the association of severe acne with breast cancer. We observed that the use of antibiotics for acne was associated with a higher breast cancer risk, while use of Accutane was not. However, misclassification of the antibiotic exposure was likely. For example, some participants reported using antibiotics for a combination of reasons, e.g., "acne and rosacea" or ambiguous reasons, e.g., "zits." We also assumed that everyone who did not explicitly report using antibiotics for acne was a non-user, which may not be accurate. Accutane first became available in 1982, meaning that most Sister Study participants would not have had access to it during adolescence. Furthermore, because it cost several hundred dollars per month [29], its use might have been limited to wealthier women or women with good health insurance. In our sample, only 28% of women who took Accutane also reported severe acne. This suggests that Accutane was prescribed for less severe acne during the early years of its availability, at least among those who could afford it, which could explain why the association with breast cancer was more modest when Accutane was included in the exposure definition. It is also plausible that Accutane protects against breast cancer by reducing circulating levels of several hormones, including testosterone [30], thereby mitigating the positive association between severe acne and breast cancer risk.

To assess sensitivity to hormonal disorders, we ran analyses excluding women who reported having PCOS, which increases circulating androgen levels in women and is associated with acne [17]. The resulting HR was nearly identical to the original estimate, likely because extremely few women in our study sample (about 2.5%) reported having PCOS.

The association between invasive breast cancer and severe acne was very similar to that for DCIS, indicating no clear difference by disease stage. This provides evidence against the idea that the observed association is driven by screening bias, which could have resulted if women with better access to medical care were more likely to seek both treatment for their acne and regular mammograms. Results from other sensitivity analyses, such as excluding women who had had prophylactic mastectomy, and adjusting for oophorectomy status, were consistent with our main findings.

This study population is predominately non-Hispanic White and well-educated, which may limit the generalizability of our findings. Additionally, all participants in the Sister Study have a family history of breast cancer, which means they are already at higher risk of the disease [31, 32]. However, this risk-based sampling method enriches the Sister Study cohort for breast cancer endpoints and relevant exposures and is well-suited for studying breast cancer risk factors [28]. We observed no clear differences in

Table 2 Acne diagnosis, acne treatment and breast cancer risk, NIEHS Sister Study 2003–2009

	Non-cases $N=47{,}127$[a]	Breast cancer cases (invasive or DCIS) $N=3019$[a]	Minimally-adjusted HR[b]	Fully-adjusted HR[c]
Ever diagnosed with severe/cystic scarring acne; *N* (%)				
No	46,122 (98)	2943 (97)	Ref	Ref
Yes	1005 (2)	76 (3)	1.22 (0.97, 1.54)	1.23 (0.98, 1.54)
Acne/blemish product use ages 10–13; *N* (%)				
Never	23,001 (51)	1458 (51)	Ref	Ref
Sometimes	15,231 (34)	994 (34)	1.05 (0.96, 1.14)	1.02 (0.94, 1.11)
Frequently	6326 (15)	430 (15)	1.11 (0.99, 1.24)	1.07 (0.96, 1.20)
				p trend = 0.25
Age first diagnosed with severe/cystic scarring acne; *N* (%)				
Never	46,122 (98)	2943 (97)	Ref	Ref
< 18	465 (1)	42 (1)	1.39 (1.02, 1.89)	1.40 (1.04, 1.90)
≥ 18	534 (1)	34 (1)	1.08 (0.77, 1.52)	1.08 (0.77, 1.51)
				p heterogeneity = 0.25
Diagnosed with severe/cystic acne before first pregnancy; *N* (%)				
Never had severe acne	46,122 (98)	2943 (97)	Ref	Ref
Before first pregnancy	746 (2)	58 (2)	1.24 (0.95, 1.61)	1.24 (0.95, 1.60)
After first pregnancy	254 (1)	18 (1)	1.22 (0.77, 1.93)	1.23 (0.78, 1.96)
				p heterogeneity = 1.0
Severe and adolescent acne[d]; *N* (%)				
No	46,690 (99)	2982 (99)	Ref	Ref
Yes	423 (1)	36 (1)	1.37 (0.99, 1.90)	1.35 (0.97, 1.87)
Ever used Accutane for acne; *N* (%)				
No	45,188 (96)	2885 (96)	REF	REF
Yes	1817 (4)	128 (4)	1.17 (0.98, 1.40)	1.17 (0.98, 1.39)
Ever had severe/cystic acne diagnosis OR used Accutane; *N* (%)				
No	44,538 (94)	2834 (94)	Ref	Ref
Yes	2623 (6)	190 (6)	1.19 (1.02, 1.38)	1.17 (1.00, 1.35)
Ever used antibiotics[e] for acne; *N* (%)				
No	44,538 (94)	2834 (94)	Ref	Ref
Yes	2623 (6)	190 (6)	1.19 (1.02, 1.38)	1.17 (1.00, 1.35)

Missing: ever severe/cystic acne (34 non-cases, 5 cases), acne products age 10–13 (2603 non-cases, 142 cases), age at acne diagnosis (40 non-cases, 5 cases), acne before first pregnancy (39 non-cases, 5 cases), severe and adolescent acne (48 non-cases, 6 cases), Accutane use (142 non-cases, 9 cases), severe acne and Accutane (156 non-case, 11 cases)

[a]Participants with complete confounder information for full adjustment

[b]Hazard ratios adjusted for race/ethnicity and participant's head of household's highest educational attainment when the participant was 13 years old

[c]Hazard ratios adjusted for race/ethnicity, participant's highest educational attainment at baseline, age at menarche, body mass index, menopausal status at baseline, interaction between body mass index and menopausal status, parity, duration of hormonal contraceptive use, hormone therapy use, smoking, alcohol use, and age at first birth (as interaction term with parity)

[d]Women reporting both severe acne diagnosis and frequent use of acne/blemish products ages 10–13

[e]Includes oral and topical antibiotics. Those not reporting antibiotic usage were assumed to be non-users

the effect estimates by degree of family history. Moreover, Zhang et al.'s similar result from the Nurses' Health Study II, whose participants were not recruited based on their family history, suggests that our findings are externally valid.

Misclassification of exposure was a concern in this study, as severe acne usually occurs during adolescence or early adulthood, meaning that participants were likely reporting their exposure many years after it happened. However, we

Table 3 Stratified adjusted[a] hazard ratios (HRs) for their associations between severe acne and breast cancer in the Sister Study

	Number of cases	Severe/cystic acne diagnosis		Severe and adolescent acne	
		HR (95% CI)	Heterogeneity *p* value	HR (95% CI)	Heterogeneity *p* value
Time-varying menopausal status					
Premenopausal	560	1.25 (0.79, 2.00)	0.90	1.16 (0.55, 2.44)	0.67
Postmenopausal	2459	1.21 (0.94, 2.12)		1.39 (0.96, 2.00)	
Race					
Non-Hispanic White	2602	1.22 (0.96, 1.56)	0.95	1.30 (0.92, 1.83)	0.35
Other	422	1.25 (0.63, 2.51)		2.27 (0.74, 6.95)	
Parity					
Nulliparous	557	1.12 (0.69, 1.81)	0.66	1.04 (0.49, 2.18)	0.43
Parous	2467	1.26 (0.98, 1.64)		1.45 (1.01, 2.09)	
Body mass index (BMI)					
Non-obese (<30 kg/m^2)	2084	1.27 (0.97, 1.65)	0.63	1.42 (0.97, 2.06)	0.55
Obese (≥ 30 kg/m^2)	940	1.11 (0.71, 1.75)		1.12 (0.56, 2.21)	
Ever hormone therapy use					
No	1639	1.25 (0.93, 1.67)	0.85	1.38 (0.91, 2.09)	0.85
Yes	1385	1.19 (0.83, 1.73)		1.29 (0.76, 2.20)	
Ever hormonal contraceptive use					
No	478	0.87 (0.39, 1.94)	0.37	1.89 (0.72, 4.98)	0.48
Yes	2546	1.27 (1.00, 1.61)		1.30 (0.92, 1.84)	
Age at menarche					
Not early (≥ 12)	2356	1.17 (0.89, 1.53)	0.43	1.25 (0.84, 1.87)	0.47
Early (<12)	668	1.43 (0.93, 2.21)		1.62 (0.92, 2.85)	
Family history of breast cancer					
1 affected sister or half-sister	1957	1.30 (0.99, 1.71)	0.46	1.37 (0.93, 2.01)	0.88
≥ 2 affected 1st degree relatives	1067	1.08 (0.72, 1.63)		1.29 (0.70, 2.39)	

[a]Hazard ratios adjusted for race/ethnicity, participant's highest educational attainment at baseline, age at menarche, body mass index (as a restricted cubic spline), menopausal status at baseline, interaction between body mass index and menopausal status, parity, duration of hormonal contraceptive use, hormone therapy use, smoking, alcohol use and age at first birth

expect misclassification would be non-differential by case status and thus any related bias would be towards the null.

A strength of our study was its large sample size, which gave us sufficient power to analyze rare exposures such as severe acne and to stratify by age at acne diagnosis. The prospective design, under which only new breast cancer cases were observed, enabled confirmation that exposure (severe acne) preceded disease. This established temporality and avoided recall bias. We also considered numerous severe acne exposure definitions and found consistent estimates of the association with breast cancer, which strengthens our confidence in the association. Finally, the Sister Study collected a wealth of data on potential confounders for which we could adjust our regression models to obtain more accurate effect estimates.

Conclusion

Our study offers further evidence that severe acne may be positively associated with breast cancer risk. Our findings are consistent with prior evidence to support a role for early-life hormonal imbalance in breast cancer development, and suggest more research is needed to elucidate the specific biological mechanisms underlying this association, particularly during adolescence. If this work can be further replicated and validated, severe acne should be

Table 4 Alternative case analyses for severe acne and breast cancer in the Sister Study

	Number of included cases	Fully-adjusted[a] HR (95% CI)
Severe acne diagnosis		
Original estimate	3019	1.23 (0.98, 1.54)
Invasive breast cancer only	2339	1.22 (0.94, 1.58)
Ductal carcinoma in situ only	667	1.27 (0.80, 2.03)
Estrogen receptor negative cases only	399	1.31 (0.72, 2.40)
Estrogen receptor positive cases only	2214	1.16 (0.88, 1.52)
Severe acne diagnosis before age 18[b]		
Original estimate	3019	1.44 (1.04, 1.90)
Invasive breast cancer only	2339	1.25 (0.87, 1.80)
Ductal carcinoma in situ only	667	1.97 (1.14, 3.40)
Estrogen receptor negative cases only	399	2.02 (1.00, 4.07)
Estrogen receptor positive cases only	2214	1.25 (0.86, 1.82)
Frequent acne/blemish product use ages 10–13 and severe/cystic acne diagnosis		
Original estimate	3018	1.35 (0.97, 1.87)
Invasive breast cancer only	2339	1.42 (0.98, 2.04)
Ductal carcinoma in situ only	666	1.13 (0.54, 2.38)
Estrogen receptor negative cases only	399	1.61 (0.72, 3.62)
Estrogen receptor positive cases only	2213	1.26 (0.85, 1.86)

[a]Hazard ratios adjusted for race/ethnicity, participant's highest educational attainment at baseline, age at menarche, body mass index, baseline menopausal status, interaction between body mass index and menopausal status, parity, duration of hormonal contraceptive use, hormone therapy use, smoking, alcohol use and age at first birth

[b]Relative to no severe acne diagnosis ever

considered, along with other risk factors, as a possible predictor of future breast cancer risk.

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Complains with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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