



# Sexual orientation and benign breast disease in a cohort of U.S. women

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## Abstract

**Purpose** Several studies indicate that sexual minority (e.g., bisexual, lesbian) women may be at an increased risk for breast cancer. However, we know little about how risk factors, such as benign breast disease (BBD)—which can confer nearly a fourfold breast cancer risk increase—may vary across sexual orientation groups.

**Methods** Among Nurses' Health Study II participants followed from 1989 to 2013 ( $n = 99,656$ ), we investigated whether bisexual and lesbian women were more likely than heterosexual women to have breast cancer risk factors including a BBD diagnosis (self-reported biopsy or aspiration confirmed,  $n = 11,021$ ). Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

**Results** Compared to heterosexuals, sexual minority participants more commonly reported certain breast cancer risk factors including increased alcohol intake and nulliparity. However, sexual minority participants were more likely than heterosexuals to have certain protective factors including higher body mass index and less oral contraceptive use. When evaluating age- and family history-adjusted rates of BBD diagnoses across sexual orientation groups, bisexual (HR 1.04, 95% CI [0.78, 1.38]) and lesbian (0.99 [0.81, 1.21]) women were just as likely as heterosexuals to have a BBD diagnosis. Results were similar after adjusting for other known breast cancer risk factors.

**Conclusions** In this cohort of women across the U.S., sexual minorities were more likely than heterosexuals to have some breast cancer risk factors—including modifiable risk factors such as alcohol intake. Heterosexual, bisexual, and lesbian women were equally as likely to have a BBD diagnosis.

**Keywords** Sexual and gender minorities · Health status disparities · Breast neoplasms · Breast diseases · Alcohol drinking

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## Introduction

Emerging research shows sexual minority (e.g., bisexual, lesbian) women are at an increased risk for breast cancer compared to heterosexual women [1]. Data have been limited to explore the origin of these disparities since sexual orientation measures are not collected in cancer registries [2, 3]. Recently, researchers have used different approaches to overcome this dearth of data. For example, researchers have documented that geographic areas with a greater density of lesbian women have a higher incidence of breast cancer [4]. Prediction models reveal lesbian women have a higher probability of developing breast cancer compared to their heterosexual sisters [5]. In regards to breast cancer mortality, women in same-sex households appear more likely to die from breast cancer compared to women in different-sex households [6].

Compared to heterosexual women, sexual minority women may have an adverse risk factor profile for breast cancer including more nulliparity, alcohol use, and obesity compared to heterosexual women [7–12]. However, it is unclear how these risk factors as well as others such as benign breast disease (BBD)—which can confer a significant breast cancer risk increase—may vary across sexual orientation groups. Certain BBD subtypes, such as proliferative BBD, are associated with nearly a fourfold increase in breast cancer risk [13]. Therefore, it is important that sexual orientation-related disparity research examine BBD, including different subtypes. Sexual minorities could be at an increased risk for BBD through a number of pathways. In part due to the stress of experiencing discrimination, sexual minority adolescents are more likely than heterosexuals to use alcohol [14] and less likely to be physically active [15–17], two risk factors for BBD [18, 19].

We used data from a large U.S. longitudinal cohort study to examine breast cancer risk factors and BBD diagnoses across sexual orientation groups. Longitudinal cohort studies with substantial statistical power and high-quality assessments of sexual orientation and cancer endpoints are the best way to fill existing research gaps. Such studies provide the empirical evidence needed to develop public health interventions and offer data that are difficult for cancer registries to collect, such as self-reported alcohol intake. To our knowledge, this is the first study to examine sexual orientation in relation to the risk of BBD.

## Methods

### Study population

Data were drawn from the Nurses' Health Study II (NHSII), a prospective cohort study that began in 1989 when female nurses aged 25 to 42 years completed questionnaires about their health. Follow-up questionnaires continue to be sent biennially. The cumulative follow-up on each questionnaire cycles is over 90%. Of the 116,429 participants at baseline, we excluded 14,716 participants who did not complete either questionnaire on which sexual orientation was assessed (described below), and we also excluded 1,655 participants who completed such a questionnaire but skipped the sexual orientation measure. Additionally, the current analysis was limited to participants who reported their sexual orientation as heterosexual, bisexual, or lesbian so we excluded 402 additional participants who endorsed other responses (e.g., "prefer not to respond"), resulting in a total sample size of 99,656. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

### Measures

#### Sexual orientation

In 1995 and 2009, the following measure was included on the NHSII questionnaire, after being pilot tested [20]: "Whether or not you are currently sexually active, what is your sexual orientation or identity? (Please choose one answer). (1) Heterosexual, (2) Lesbian, gay, or homosexual, (3) Bisexual, (4) None of these, (5) Prefer not to answer." For these analyses, we used the most recent report of sexual orientation from 2009 but if these data were missing, we imputed (e.g., carried forward) the 1995 response. Sexual orientation groups were modeled as heterosexual (reference), bisexual, or lesbian. To increase statistical power, we conducted sensitivity analyses by modeling sexual orientation in different ways such as combining bisexual and lesbian participants into a single sexual minority group.

#### Benign breast disease

Starting on the baseline questionnaire in 1989 and continuing on each subsequent questionnaire, participants reported any physician diagnosis of fibrocystic or other BBD as well as whether the diagnosis was confirmed by biopsy and/or aspiration. We also requested biopsy samples from a subsample of the participants with self-reported diagnoses

between 1993 and 2003. Study pathologists conducted independent blinded review of the biopsy samples and classified BBD lesions according to the Dupont and Page criteria [21] as: non-proliferative, proliferative without atypia, and proliferative with atypia (atypical ductal hyperplasia and atypical lobular hyperplasia).

To maximize statistical power in the sexual orientation subgroups, the primary outcome for this analysis was self-reported biopsy and/or aspiration confirmed BBD. Within the subsample of participants who provided biopsy samples, we conducted secondary analyses of the biopsy-confirmed BBD categories (combined and separately) of: (1) non-proliferative; and (2) proliferative (with and without atypia). Secondary analyses also examined BBD among participants with and without a mammogram as well as among participants with and without a family history of breast cancer.

### Covariates

Potential confounders included age (months) and family history of breast cancer in a mother or sister (assessed in 1989, 1997, 2001, 2005, and 2009). Sensitivity analyses were conducted that adjusted for other known BBD risk factors, which could lie on the causal pathway between sexual orientation and BBD (e.g., age at menarche [ $< 12$ , 12, 13, 14,  $> 14$  years], body mass index [BMI] at age 18 years [ $< 18.5$ , 18.5–22.4, 22.5–24.9, 25–29.9,  $\geq 30$ ], weight change since age 18 years [pounds], alcohol intake [no alcohol,  $< 5$ , 5–10,  $> 10$  g/day], adolescent alcohol intake [no alcohol,  $< 5$ , 5–10,  $> 10$  grams/day], height [meters], oral contraceptive use [never, past, current], parity [i.e., pregnancies  $\geq 20$  weeks gestation; nulliparity, 1–2,  $\geq 3$  children], age at first birth [years], total duration of breastfeeding across all pregnancies [ $< 1$ , 1–3, 3–12,  $> 12$  months], hormone therapy use [none, oral estrogen, oral estrogen plus progesterone, other formulations], and menopausal status [premenopausal, postmenopausal]). If any covariate data were missing, we imputed data from previous years.

### Statistical analysis

Participants contributed person-time from baseline in 1989 until return of the most recent questionnaire in 2015. Women were then followed from entry into the cohort until biopsy and/or aspiration confirmed BBD or death. Cox proportional hazards models were stratified by calendar time with age (months) as the timescale to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of developing BBD. The Lunn and McNeil [22] approach was used to compare different BBD categories to account for competing risks. The proportional hazard assumption was assessed using a likelihood ratio test for the interaction between sexual orientation and age.

## Results

Of the 99,656 participants in our sample, 98.7% ( $n = 98,315$ ) identified as heterosexual, 0.4% ( $n = 415$ ) as bisexual, and 0.9% ( $n = 926$ ) as lesbian (see Table 1). Compared to heterosexuals, bisexual and lesbian participants more commonly reported certain breast cancer risk factors including taller height and higher alcohol intake (current and during adolescence, all  $p < 0.0008$ ). The largest sexual orientation difference in breast cancer risk factors related to parity with bisexuals (51%) and lesbians (74%) being more likely than heterosexuals (30%) to be nulliparous. In contrast, bisexual and lesbian participants were more likely than heterosexuals to have certain protective factors against breast cancer including higher body mass index, less oral contraceptive use, and a younger age at first birth (all  $p < 0.0001$ ). There were no sexual orientation differences ( $p > 0.05$ ) in family history of breast cancer, weight change since age 18 years, age at menarche, menopausal status, or hormone therapy use. Additionally, there were no sexual orientation differences in breastfeeding duration (among parous women) but when parity is considered, sexual minorities have less of this protective factor.

A total of 11,021 participants self-reported they had biopsy or aspiration confirmed BBD (see Table 2). Study pathologists reviewed biopsy specimens from a subset of these cases ( $n = 2,004$ ) to classify lesions as either non-proliferative ( $n = 671$ ) or proliferative (including with and without atypia;  $n = 1,333$ ).

When evaluating rates of BBD diagnoses across sexual orientation groups, bisexual (HR 1.04, 95% CI [0.78, 1.38]) and lesbian (0.99 [0.81, 1.21]) women were just as likely as heterosexuals to have a BBD diagnosis. These estimates were consistent even after adjusting for known breast cancer risk factors. Additionally, there were no differences by sexual orientation in BBD subtype. These estimates were all similar in all sensitivity analyses where we combined bisexual and lesbian participants, where we restricted to participants with a mammogram, where we stratified by those with and without a family history of breast cancer, and where we adjusted for other known BBD risk factors.

## Discussion

For almost 20 years, the Institute of Medicine [23, 24] has warned of a potential elevated breast cancer risk among sexual minorities. Without information on sexual orientation in cancer registries, researchers have had to apply novel methodological approaches to examine potential

**Table 1** Select characteristics of women in the Nurses' Health Study II at baseline in 1989 by sexual orientation ( $n=99,656$ )

	Heterosexual (98.7%, $n=98,315$ )	Bisexual (0.4%, $n=415$ )	$p^1$	Lesbian (0.9%, $n=926$ )	$p^1$
Age, mean years (SD); Range: 24–44	34.4 (4.7)	34.9 (4.7)	0.07	35.1 (4.5)	<.0001
Family history of breast cancer, % ( $n$ )	15.7 (15,439)	18.3 (76)	0.14	17.4 (161)	0.16
Height, mean meters (SD)	1.6 (0.1)	1.7 (0.1)	0.20	1.7 (0.1)	0.0008
Body mass index at age 18 years, $\text{kg}/\text{m}^2$ (SD)	21.2 (3.3)	22.2 (4.2)	<.0001	22.4 (4.0)	<.0001
Weight change since age 18 years, mean lbs (SD)	16.8 (23.3)	19.0 (27.0)	0.06	17.9 (25.5)	0.16
Alcohol intake, % ( $n$ )			<.0001		<.0001
No alcohol	42.6 (36,427)	35.7 (129)		30.4 (247)	
0–5 g per day	39.0 (33,377)	37.7 (136)		37.2 (302)	
5 to 10 g per day	9.7 (8,275)	10.6 (38)		14.4 (117)	
> 10 g per day	8.8 (7,500)	16.1 (58)		18.1 (147)	
Oral contraceptive use, % ( $n$ )			0.16		<.0001
Never	16.2 (15,897)	17.4 (72)		38.5 (355)	
Past	71.0 (69,754)	72.9 (301)		58.0 (535)	
Current	12.8 (12,564)	9.7 (40)		3.5 (32)	
Parity, % ( $n$ )			<.0001		<.0001
Nulliparity	29.6 (29,073)	50.6 (210)		74.4 (689)	
1–2 children	52.4 (51,459)	42.2 (175)		20.4 (189)	
$\geq 3$ children	18.1 (17,769)	7.2 (30)		5.2 (48)	
Age at first birth, among parous, mean (SD)	25.5 (4.0)	25.1 (5.0)	0.14	24.2 (4.1)	<.0001
Breastfeeding, among parous % ( $n$ )			0.28		0.26
< 1 month	21.1 (13,425)	16.9 (32)		22.7 (49)	
1–3 months	6.7 (4,240)	4.8 (9)		5.6 (12)	
3–12 months	31.1 (19,788)	35.5 (67)		36.7 (78)	
> 12 months	41.1 (26,180)	42.9 (81)		35.7 (77)	

<sup>1</sup> $p$  calculated using chi squared tests for categorical variables and ANOVA for continuous variables

disparities. For the current analyses, we leveraged longitudinal cohort data from women across the U.S. and we found that bisexual as well as lesbian women were more likely than heterosexual women to have some breast cancer risk factors though also more likely to have some protective factors. However, heterosexual, bisexual, and lesbian women were equally as likely to have a BBD diagnosis.

A previous analysis in the NHSII cohort revealed that sexual minority participants appeared to be at an increased risk of breast cancer. Austin et al. used the Rosner–Colditz Risk Prediction Model to identify significantly elevated rates of breast cancer risk in both bisexual (mean predicted 1-year breast cancer incidence rate ratio, 1.10; 95% CI 1.10, 1.10) and lesbian women (1.06; 95% CI 1.06, 1.06) compared with heterosexual women [25]. It is now imperative that we identify contributing risk factors to these potential breast cancer disparities.

Research on other sexual orientation-related cancer disparities have focused on established risk factors like nulliparity, obesity, and alcohol [7–9]. One systematic review [8] pooled the prevalence estimates of risk factors from seven independent surveys of bisexual and lesbian women

to compare with national estimates (likely based on samples predominantly of heterosexual women). In alignment with the current findings, bisexual and lesbian women in the NHSII sample had a higher prevalence of a number of breast cancer risk factors compared to heterosexual women.

Our study did not identify sexual orientation differences in BBD diagnoses. This could happen for a number of reasons. There truly may not be sexual orientation differences or we may not have been able to observe these differences due to methodological limitations. While the large sample size of NHSII was powerful, it may not have been large enough to detect small effect estimates. Second, our measure of sexual orientation was limited to capturing participants' sexual orientation identity and did not assess the two other dimensions of sexual orientation (i.e., sex of sexual partners and sex of romantic attractions). As a result, participants who identify as heterosexual but who also have had same-sex partners or same-sex romantic attractions were included in the reference group, which may have biased our results towards the null. Future research should explore breast cancer risk factors, including BBD diagnoses, across all three dimensions of sexual orientation. Sexual minority

**Table 2** Benign breast disease (BBD) risk in the Nurses' Health Study II by sexual orientation ( $n=99,656$ )

Sexual orientation	Cases/ person-years	Age- and family history-adjusted Cox proportional model hazard ratio (95% CI)	Multivariable <sup>1</sup> adjusted Cox proportional model hazard ratio (95% CI)
Self-reported biopsy or aspiration confirmed BBD			
Heterosexual	10,875/1,832,530	1.0 (ref)	1.0 (ref)
Bisexual	47/7,627	1.04 (0.78, 1.38)	1.04 (0.77, 1.40)
Lesbian	99/16,853	0.99 (0.81, 1.21)	1.00 (0.81, 1.23)
Subsample with BBD biopsy specimens <sup>2</sup>			
Heterosexual	1,977/1,839,910	1.0 (ref)	1.0 (ref)
Bisexual	8/7,661	0.96 (0.48, 1.93)	1.03 (0.52, 2.07)
Lesbian	19/13,925	1.03 (0.65, 1.62)	1.09 (0.68, 1.75)
Subsample with BBD biopsy specimens <sup>2</sup> —Non-proliferative BBD			
Heterosexual	662/1,841,137	1.0 (ref)	1.0 (ref)
Bisexual	3/7,668	1.11 (0.36, 3.46)	1.18 (0.38, 3.69)
Lesbian	6/16,939	0.97 (0.43, 2.17)	1.10 (0.49, 2.49)
Subsample with BBD biopsy specimens <sup>2</sup> —Proliferative BBD with and without atypia			
Heterosexual	1,315/18,40,500	1.0 (ref)	1.0 (ref)
Bisexual	5/7,663	0.89 (0.37, 2.15)	0.96 (0.40, 2.32)
Lesbian	13/16,930	1.06 (0.61, 1.83)	1.08 (0.61, 1.92)

<sup>1</sup>Multivariable model adjusted for age, family history, age at menarche, BMI at age 18 years, weight change since age 18 years, alcohol intake, adolescent alcohol intake, height, oral contraceptive use, parity, age at first birth, breastfeeding, hormone therapy use, and menopausal status

<sup>2</sup>Biopsy specimens available only on participants who reported physician-diagnosed BBD between 1993 and 2003 and who also gave permission to review biopsy records and pathology slides

women consistently report employment discrimination and less healthcare access than heterosexual women [26–28] but results have been mixed on sexual orientation-related mammography screening utilization; some results—including from NHSII [29]—indicate sexual minority women are less likely to undergo screening [8, 9, 30] while there are no sexual orientation differences in other samples [31, 32]. Given that BBD is often diagnosed through mammography, disparities in healthcare access may lead to an underestimate of BBD among sexual minority women. However, when we restricted our results to participants who reported mammography, the results did not substantially change.

Our study is the first to our knowledge to examine sexual orientation and BBD, but there are a number of limitations. This sample included only nurses and was limited in terms of racial/ethnic diversity. While our findings may not generalize to other populations, the homogeneous nature of this sample is also a strength in that confounding—such as by socioeconomic status and race/ethnicity—is reduced. However, it is critical that future research examine sexual orientation differences among non-nursing populations who may have less access to healthcare as well as more racially/ethnically diverse populations, particularly given the known racial/ethnic disparities in breast cancer [33]. While NHSII is a large cohort, we do not yet have enough cases to investigate disparities in breast cancer across sexual orientation groups. Future research on BBD and breast cancer should

also explore protective factors that may be more or less common among sexual minorities such as chemoprevention and reduction mammoplasty, on which we had limited data. We also lacked detailed family history data other than breast cancer diagnoses among the participants' mother or sisters; future work could explore a broader definition with the inclusion, for example, of daughters. These limitations were countered by the high-quality disease data including the role of experienced breast pathologists in defining BBD outcomes as well as the review of biopsy samples. Findings were also strengthened by various sensitivity analyses including restricting analyses to women with mammograms to address any potential sexual orientation disparities in screening and detection. In the first study to investigate the association between sexual orientation and risk of BBD, our approach was also strengthened by our ability to adjust for time-varying covariates.

While we did not identify disparities in BBD diagnoses between sexual minority and heterosexual women, a number of breast cancer risk factors were different between sexual orientation groups. Targeted interventions are needed to reduce the elevated breast cancer risk factors among sexual minorities including alcohol use, which may be contributing to breast cancer disparities. Additionally, sexual minorities face unique issues, such as employment discrimination, resulting in less access to health insurance which may result in less mammographic screenings compared to heterosexuals

[26–28]. Therefore, more work is needed to help sexual minority women overcome the many barriers they face in accessing care and reducing their breast cancer risk. Without such changes, sexual minorities may continue to be disproportionately burdened by breast cancer.

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