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Application of the Rosner-Colditz Risk Prediction Model to Estimate Sexual Orientation Group Disparities in Breast Cancer Risk in a U.S. Cohort of Premenopausal Women

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Abstract

Background—Lesbian and bisexual women may be at greater risk of breast cancer than heterosexual women during the premenopausal period due to disparities in risk factors.

Methods—With 16 years of prospective data from a large cohort of U.S. women ages 25–58 years, we conducted a breast cancer risk assessment for 87,392 premenopausal women by applying the Rosner-Colditz biomathematical risk-prediction model to estimate breast cancer risk based on known risk factors. Based on each woman's comprehensive risk factor profile, we calculated the predicted one-year incidence rate (IR) per 100,000 person-years and estimated incidence rate ratios (IRR) and 95% confidence intervals (CI) for lesbian and bisexual women compared to heterosexual women.

Results—87,392 premenopausal women provided 1,091,871 person-years of data included in analyses. Mean predicted one-year breast cancer IRs per 100,000 person-years for each sexual orientation group were: heterosexual 122.55, lesbian 131.61, and bisexual 131.72. IRs were significantly elevated in both lesbian (IRR 1.06; 95 CI 1.06, 1.06) and bisexual (IRR 1.10; 95% CI 1.10, 1.10) women compared to heterosexual women.

Conclusions—Our findings suggest both lesbian and bisexual women have slightly elevated predicted breast cancer incidence compared to heterosexual women throughout the premenopausal period.

Impact—Health professionals must ensure that breast cancer prevention efforts are reaching these women. As more health systems around the country collect data on patient sexual orientation, the National Cancer Institute's SEER cancer registry should add this information to its data system to

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monitor progress in reducing sexual orientation-related disparities in cancer incidence and mortality.

Keywords

breast cancer; risk model; sexual orientation; bisexual; lesbian; premenopausal

Introduction

Breast cancer is among the most commonly diagnosed cancers in U.S. women (1), and one group that stands out as potentially at elevated risk is lesbian and bisexual women (2–7). Recent research has identified a constellation of risk factors, including overweight, nulliparity, and alcohol use, that may place lesbian and bisexual women at greater lifetime risk than heterosexual women for developing breast cancer (8–10). Given the morbidity and mortality associated with breast cancer in U.S. women and the evidence of disparities adversely affecting lesbian and bisexual women, there is a need for new epidemiologic research into the cancer risks in this underserved and understudied population.

There are few epidemiologic studies that are both large enough and include appropriate measures of sexual orientation to provide data on sexual orientation patterns in breast cancer incidence. For sociodemographic groups defined by age, sex, race/ethnicity, socioeconomic status, and region of residence, the U.S. National Cancer Institute's registry Surveillance Epidemiology and End Results (SEER) gathers information needed to monitor cancer incidence, mortality, and disparities by race/ethnicity, region, gender, and age. SEER does not include information on sexual orientation in its data system, however, so this data source contributes little to understanding of sexual orientation disparities in cancer incidence rates and mortality (11, 12).

In lieu of SEER data on incidence rates, researchers have developed other approaches to estimate breast cancer disparities associated with sexual orientation. Cochran et al. compared self-reported breast cancer history among lesbian and bisexual women ages 18 to 75 in a pooled analysis of six surveys to similar self-report data collected from women in National Health and Nutrition Examination Survey III (5). They did not find significant differences in self-reported history of breast cancer. Boehmer et al. linked data on breast cancer incidence rates from SEER to U.S. Census 2000 data on population density of female same-sex partnered households, a proxy for lesbian population density, in the 215 counties covered by the SEER registry (13). Based on their ecological analyses, the authors estimate that a one-unit increase in the density of female same-sex partnered households in a county is associated with a 13% higher rate of breast cancer cases, which is consistent with an interpretation that lesbians may have elevated incidence of breast cancer compared to heterosexual women.

Researchers have sought to compensate for inadequate national collection of incidence data by estimating the risk of breast cancer in lesbian and bisexual women relative to heterosexual women using mathematical modeling techniques. Three research teams have used the Gail breast cancer risk model (14), a statistical method for calculating a woman's five-year and lifetime risk of breast cancer, to estimate orientation group differences in risk (9, 15, 16). Dibble et al. applied the Gail model to data gathered from a California sample of lesbians matched in dyads with their heterosexual sisters ages 40 years and older (mean age 49 years) (9), and Brandenburg et al. applied the Gail model to data from a sample of lesbian and heterosexual women ages 18 to over 60 years old (mean age 43 years) recruited from Chicago, New York City, and Minneapolis-St. Paul (16). Both studies estimated that lesbians had a higher five-year and lifetime breast cancer risk compared to heterosexual

women (9, 16). McTiernan and colleagues also applied the Gail model to estimate breast cancer risk in a Seattle-based sample of lesbians compared to women in the general population ages 18–74 years (mean age 42 years) but did not find lesbians to be at elevated predicted risk (15). These studies were based on cross-sectional survey data, and none estimated risk separately for bisexual women or for specific periods defined by age or menopausal status.

While the Gail model has been shown to be a useful prediction tool for estimating breast cancer risk (17), limitations of the model are that it does not fully account for exposure effects that vary with time and reproductive status history and it overestimates risk in premenopausal women by as much as twofold (18). It has become increasingly clear that some exposures that affect breast cancer risk, particularly body mass index (BMI), nulliparity, and age at first live birth, change in magnitude and, in some cases, direction of effect over the life course (19–23). To account for these complex exposure-disease relationships, the Rosner-Colditz risk prediction model has been developed as a risk assessment tool to expand upon the Gail model to assess exposure effects that vary by time and reproductive status history in a way that accounts for changes in both magnitude and direction of effect for certain exposures (21, 24). In addition to risk factors considered in the Gail model, the Rosner-Colditz model accounts for other important exposures, including subsequent births following the first live birth, type of and age at menopause, height, current weight, weight at age 18, and alcohol consumption (21, 24). The Rosner-Colditz model has been found to perform better than the Gail model in estimating breast cancer risk in women in a large prospective cohort study of women (18, 21, 24).

The Rosner-Colditz biomathematical model is based on the assumption that incidence of breast cancer is proportional to the number of breast cell divisions accrued through the life course up to a specified age (21, 24). The log of the rate of breast cell divisions is treated in the mathematical model as a linear function of risk factors for breast cancer that have been shown in prior research to be relevant at particular ages or periods in a woman’s life. The regression coefficients corresponding to each risk factor included in the mathematical model represent the effect of that risk factor at a particular age or period. Parameters for each exposure in the model are interpreted as relative risks. Compared to conventional logistic regression models, these models allow for more efficient testing of complex time-dependent etiologic hypotheses.

Full consideration of exposures with time- and reproductive-status varying effects on disease risk is critical for studies of lesbian and bisexual women because it is precisely these exposures for which large sexual orientation group differences have been observed (8–10, 12). Importantly, evidence suggests that lesbian and bisexual compared to heterosexual women experience higher rates of at least two risk factors – adiposity and nulliparity – that have complicated time-variant implications for breast cancer (8–10, 12). The specific aim of our study was to conduct a breast cancer risk assessment for premenopausal women of diverse sexual orientations by applying the Rosner-Colditz risk prediction model to estimate breast cancer risk as it evolves over time for each sexual orientation subgroup from age 25 to 58 years in a large, national longitudinal cohort of U.S. female nurses. We hypothesized that lesbian and bisexual women would have higher predicted incidence of breast cancer. In addition, we hypothesized that the risk disparity would be lower in the younger vs. older premenopausal period due to anticipated accumulating effects of breast cancer risk factors that are disproportionately prevalent in lesbian and bisexual women.

Materials and Methods

Study sample

In 1989, a baseline questionnaire was sent to approximately 520,000 registered nurses living in 14 of the most populous U.S. states, leading to the enrollment of 116,430 women in the Nurses' Health Study (NHS) II(25). If a completed baseline questionnaire was returned, this was considered an indication of informed consent for participation in the study. Since baseline, questionnaires have been sent to the cohort every two years to gather information on disease risk factors and disease incidence. At baseline, participants were ages 25–42 years old, and the racial/ethnic breakdown was 94% white, 2% African-American, 2% Latina, and 2% Asian. Brigham and Women's Hospital and Harvard School of Public Health provided human subjects research approval.

Measures

In 1995, a measure of sexual orientation identity was added to the NHSII questionnaire (8), reading: "Whether or not you are currently sexually active, what is your sexual orientation or identity? (Please choose one answer)" with possible responses: 1) *Heterosexual*; 2) *Lesbian, gay or homosexual*; 3) *Bisexual*; 4) *None of these*; 5) *Prefer not to answer*. Heterosexual, lesbian, and bisexual women were included in this study.

Cancer History—An item asking if breast cancer has ever been diagnosed is included on every NHSII questionnaire. The National Death Index is also routinely consulted to search for deaths among women who did not respond to the questionnaires and so were unable to provide information about diagnosis of the disease. Following receipt of consent from participants or, for decedents, from a family member, all reports of cancer diagnosis are confirmed through medical record review (19). Women were excluded from analyses once they were diagnosed with any cancer other than non-melanoma skin cancer, though observations were included up to the time of a reported diagnosis.

Information about family history of breast cancer has been collected in four survey years: 1989, 1997, 2001, and 2005. Participants were asked if any of their biological relatives had been diagnosed with cancer of the breast. For breast cancer, participants are asked to indicate if the relative was their mother, sister, or maternal or paternal grandmother. History of benign breast disease was asked at each questionnaire cycle. Participants indicate whether they have ever received a diagnosis of benign breast disease and, if so, if the diagnosis was made more than 2 years prior to the survey date, during the two years between survey cycles, or during the present year.

Height was recorded at baseline in 1989. Current weight was reported on every questionnaire starting at baseline and weight at age 18 was reported once in 1989. The validity of both self-reported current weight and weight at age 18 is strong (26, 27). Body mass index (BMI) was calculated for each year of age using the standard formula of kg/m^2 beginning from age 18 years. Alcohol use has been assessed almost every survey wave. Participants report how many servings of alcohol they typically consumed per day and week in the previous year separately for beer, wine, and liquor. At baseline, participants were also asked to indicate their typical alcohol consumption in adolescence, young adulthood, and adulthood prior to enrollment in the cohort. Pregnancy history is updated every questionnaire. Data were collected separately for pregnancies six months or longer vs. those lasting less than six months. Age at menarche was collected at baseline. Participants were asked the age at which their menstrual periods began with the response options, "9 or less, 10, 11, 12, 13, 14, 15, 16, 17 or more." Participants reported their menopausal status on each questionnaire, indicating if their periods have ceased and, if yes, the reason, either naturally

or due to hysterectomy with bilateral oophorectomy, hysterectomy with one ovary removed, or hysterectomy (only uterus removed).

On the baseline questionnaire, women were asked to describe their ancestry choosing from a list of provided categories, which were coded as white, African-American, Latina, Asian-American, multiracial, and missing (28). Participants reported annual household income in 2001, which we then used to create four categories: Less than $50,000; $50,000 to less than $75,000; $75,000 to less than $100,000; and $100,000 or greater. Region of residence was updated each year a survey was returned and was coded as Northeast, South, Midwest, and West.

Statistical Analyses

Our analytic sample included premenopausal women who were ages 25–58 years old when they responded to biennial NHSII questionnaires administered from 1989 (baseline) to 2005. Age 58 years was used as the upper age limit for these analyses to ensure sufficient sample sizes of lesbian and bisexual women (the smallest subgroups) at the upper end of the age range. Given the age distribution at baseline, only a small proportion of the cohort was older than 58 years by the 2005 wave of data collection. Most variables included in the models were either updated or cumulatively updated based on repeated measures of information. When data for a variable were missing on a wave, information from prior waves was used to carry forward values or cumulatively updated averages (29) were used, as appropriate. A total of 87,392 (75.1% of the original cohort of 116,430) women provided 1,091,871 person-years of data for our analyses.

We carried out a series of analytic steps using a modified version of the Rosner-Colditz risk prediction model (21, 24). Because the oldest age included in analyses was 58 years, we did not have sufficient data from women characterizing their exposures in the postmenopausal period; therefore variables in the Rosner-Colditz model exclusively related to the postmenopausal period, such as postmenopausal hormone use, were not included, and women were excluded from analyses once they reached menopause. We used the modified model first to generate predicted one-year breast cancer incidence rates (IR) per 100,000 person-years and then to examine sexual orientation group differences. For each year in which a participant responded to a questionnaire, we calculated the predicted one-year breast cancer IR based on each woman's risk factor profile. This method allowed us to calculate the model results for each woman multiple times (i.e., one time for each returned questionnaire) using her updated risk factor profile each survey year (e.g., alcohol use reported on current questionnaire, etc.) while also carrying forward risk factor information reported on previous questionnaires as appropriate (e.g., BMI at age 18 years, age at first birth, etc.). We estimated incidence rate ratios (IRR) and 95% confidence intervals (CI) for lesbian and bisexual women compared to heterosexual women for all ages combined and within each age strata (25–34 years, 35–44 years, and 45–58 years).

In additional analyses, the proportion of predicted IRs for lesbian and bisexual women (separately) falling into each quintile was calculated, using cutoffs for risk quintiles based on heterosexual women (the referent group) in the cohort. Quintile cutoffs were defined for all age groups combined, and then separately for each of the three age strata. Note that by design, 20% of predicted IRs from heterosexual women fell within each quintile; whereas the proportion of predicted IRs from lesbian and bisexual women in each quintile could be 20% or could be higher or lower than 20%. Finally, we conducted ordinal logistic regression to examine sexual orientation group differences in the distribution of predicted IRs across the quintiles, controlling for sexual orientation, race/ethnicity, age, region of residence, and household income. Ordinal logistic models were examined with all age groups combined and generated odds ratios (OR) and 95% CI. Age-by-sexual orientation interactions were

examined in the multivariable ordinal logistic regression model. We accounted for correlated data resulting from repeated measures by using generalized estimating equation (GEE) methods using the working correlation matrix (30).

Results

Sociodemographic characteristics of the 87,392 women included in analyses are presented in Table 1. Lesbian and bisexual women made up roughly 1% of the cohort, and women of color made up 6% of the cohort. Participants lived in all regions of the United States, and about a third of the participants had an annual household income in 2001 of $100,000 or greater. During the follow-up period, 1.8% (1592 cases) of heterosexual, 2.3% (15 cases) of lesbian, and 1.9% (6 cases) of bisexual women were diagnosed with breast cancer (P=0.60; not in table).

Table 2 presents sexual orientation group means and frequencies for important breast cancer risk factors included in the Rosner-Colditz model for the premenopausal period. Compared to heterosexual women, lesbian and bisexual women had significantly fewer births, higher BMI and greater alcohol intake during premenopause, in addition to being older at baseline. In addition, compared to heterosexual women, bisexual women were taller at baseline, and lesbians had a higher prevalence of a history of benign breast disease.

Table 3 presents predicted incident cases of breast cancer in each sexual orientation group for all ages and within age strata. Mean predicted one-year breast cancer IRs per 100,000 person-years for women of all ages in each sexual orientation group were: heterosexual 122.55, lesbian 131.61, and bisexual 131.72. IRs were significantly elevated in both lesbian (IRR 1.06; 95 CI 1.06, 1.06) and bisexual (IRR 1.10; 95% CI 1.10, 1.10) women compared to heterosexual women when combining across all ages. Findings were similar within each age strata.

The Figure depicts the distribution of predicted breast cancer IR quintile membership of bisexual and lesbian women with cutoffs for quintiles based on those for heterosexual women. The distributions are first presented for each age strata (25–34 years, 35–44 years, and 45–58 years), then presented for women ages 25–58 years combined. Interaction terms for age-by-sexual orientation group were examined but were not statistically significant (P-values>0.05), therefore they were not included in the final multivariable ordinal logistic regression model estimating the odds of predicted breast cancer IR quintile membership for bisexual and lesbian women relative to heterosexual women. Results from the final model indicated that lesbian (OR 1.24; 95% CI 1.08, 1.41) and bisexual (OR 1.28; 95% CI 1.06, 1.56) women had elevated odds of being in a quintile group at higher risk of breast cancer compared to heterosexual women of similar age, race/ethnicity, geographic region, and household income (not in table).

Discussion

Breast cancer is a leading cause of morbidity and mortality in U.S. women (1), and efforts to promote prevention are critically important. Previous epidemiologic research has identified lesbian and bisexual women as potentially at elevated risk of breast cancer because of comparatively high rates of overweight (for postmenopausal breast cancer), nulliparity, and alcohol use relative to heterosexual women. Incidence of breast cancer in lesbian and bisexual women, however, is not known because of the absence of sexual orientation information in the nation’s SEER cancer registry and a lack of large prospective cohort studies of adequate sample size with appropriate measures. In this context of limited understanding of breast cancer disparities, we undertook the present study to apply the

Rosner-Colditz risk prediction model to estimate predicted breast cancer incidence based on comprehensive risk profiles of women of diverse sexual orientation. Consistent with our hypotheses, findings suggest lesbian and bisexual women are at slightly elevated predicted risk of breast cancer compared to heterosexual women throughout the premenopausal period. Counter to our hypotheses, however, we did not find evidence that age modified the association between sexual orientation and predicted breast cancer incidence during the premenopausal years.

Findings from other studies applying the Gail model (14) to generate predicted incidence estimates in lesbian and bisexual women have been variable. Three studies using the Gail breast cancer risk model have examined sexual orientation group differences in risk comparing lesbian and heterosexual women (9, 15, 16). Dibble et al.(9) and Brandenburg et al.(16) both found lesbians to have higher five-year and lifetime predicted breast cancer risk, while McTiernan et al. (15) did not find a sexual orientation-related difference in predicted risk. Our study adds to this literature in several important ways. Our estimates were: generated using the Rosner-Colditz model, which has been found to outperform the Gail model (18, 21, 24); examined for specific premenopausal age periods (ages 25 to 58 years) for which we had prospectively collected data; and provided separately for bisexual women. As a result, our study provides the strongest evidence to date that lesbian and bisexual women in the United States may experience breast cancer risk above that of heterosexual women in the premenopausal period due to the disproportionate burden of known risk factors in this population subgroup of women.

Several limitations of our study should be considered. Self-report survey data were used in analyses, and the NHSII cohort is not a representative sample of U.S. women. White women make up the vast majority of the cohort, and there were not sufficient subsample sizes of lesbian and bisexual women of color to examine whether sexual orientation-related disparities in predicted breast cancer risk estimated for the whole cohort are similar or different within specific racial/ethnic subpopulations. Due to the age distribution of the cohort, we did not have a sufficient number of observations from postmenopausal women, so analyses had to be restricted to the premenopausal period. Given the important role of exposures with time-varying effects on breast cancer and the marked increase in risk of breast cancer after menopause, sexual orientation-related disparities in the postmenopausal period may be different from those observed in our study. Because breast cancer risk increases with age, the majority of cases occur in postmenopausal women; therefore, when sample sizes are large enough and statistical power sufficient, it will be imperative that the current study be extended to include the postmenopausal period.

Breast cancer is among the most commonly diagnosed cancers in U.S. women, and it is well-documented that lesbian and bisexual women have comparatively high rates of known risk factors for the disease. Our study, which applied the sophisticated Rosner-Colditz model to the rich, prospective NHSII cohort data to estimate predicted breast cancer incidence while accounting for time-variant exposure effects, now offers the strongest evidence to date that lesbian and bisexual women may be disproportionately burdened by breast cancer. To reduce these disparities, health professionals working in breast cancer prevention must ensure that prevention efforts are reaching lesbian and bisexual women. In addition, as more health systems around the country collect data on patient sexual orientation, the National Cancer Institute’s SEER cancer registry should add this information to its data system to monitor progress in reducing sexual orientation-related disparities in cancer incidence and mortality.

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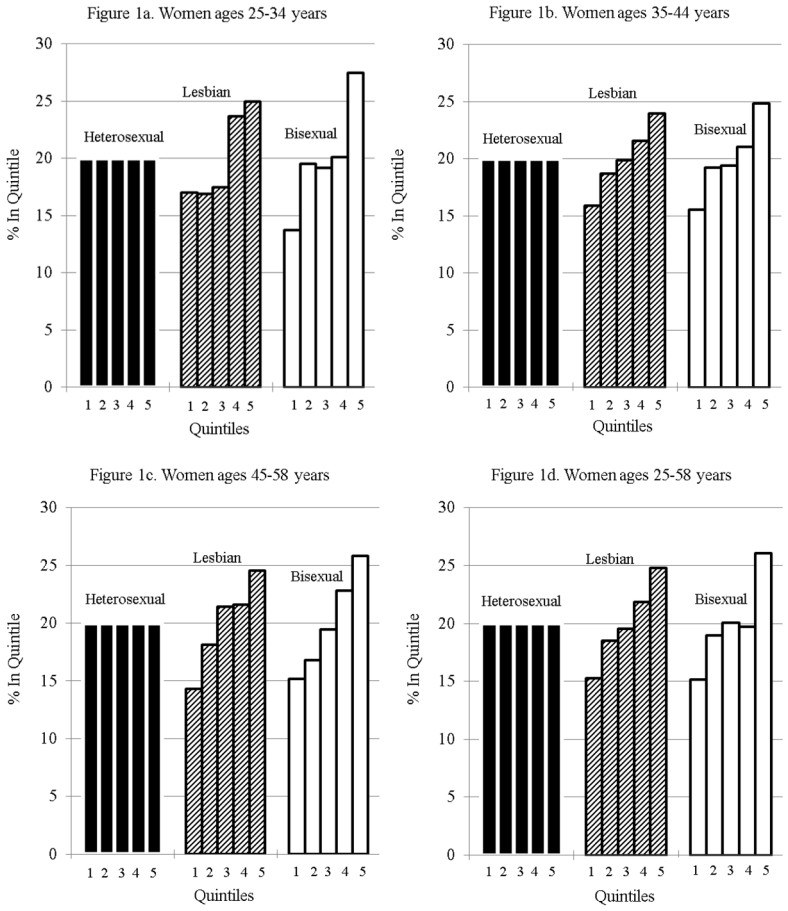

Figure.

Figures 1a–d. Sexual orientation patterns in distribution of predicted breast cancer incidence rates by risk quintiles in a U.S. cohort of women, ages 25–58 years and stratified by age group 25–34, 35–44, and 45–58 years old*

*Predicted risk quintiles are based on distribution for heterosexual women within the specified age range for Figures 1a–c and for heterosexual women ages 25–58 years for Figure 1d.

Table 1

Sociodemographic characteristics of women in the Nurses' Health Study II ages 25–42 years at baseline (N = 87,392)*

	%	n
Sexual Orientation		
Heterosexual	98.89	86,418
Lesbian	0.76	665
Bisexual	0.35	309
Race/Ethnicity		
African American	1.40	1224
Latina	1.37	1194
Asian	1.56	1367
White (non-Latina)	92.43	80,778
Other	1.80	1572
Region of Residence		
Northeast	33.44	29,154
Midwest	32.81	28,606
South	18.46	16,092
West	15.30	13,345
Household Income		
<50k	16.16	9965
50–75k	27.55	16,988
75–100k	21.24	13,100
100k+	35.05	21,611

*Percentages and Ns calculated out of nonmissing.

Table 2

Age-standardized risk factors, by sexual orientation, included in Rosner-Colditz risk prediction model to estimate disparities in breast cancer risk in a U.S. cohort of premenopausal women (number of person-years = 1,091,871)*

	Sexual Orientation				
Breast Cancer Risk Factors	**Heterosexual (person-years =1,080,419**	**Lesbian (person-years =7821)**	**P-Value+**	**Bisexual (person-years =3631)**	**P-Value+**
Age at Baseline (years)	33.62	34.42	0.0006	34.40	0.0160
Age at Menarche (years)	12.43	12.38	0.4351	12.33	0.2919
Duration of Premenopause (years)	27.47	28.03	0.0201	28.08	0.0968
Age at First Birth§	27.27	26.82	0.2808	26.78	0.2250
Number of Births	1.71	0.38	<.0001	0.98	<.0001
Mean BMI During Premenopause (kg/m^2)¥	22.04	23.28	<.0001	23.11	0.0004
Height at Baseline (inches)	64.90	65.15	0.0532	65.28	0.0139
Mean Alcohol Intake/Day During Premenopause (grams)	3.56	6.18	<0.0001	5.18	<0.0001
History of Benign Breast Disease (%)	39.99	44.59	0.0269	44.67	0.1071
Family History of Breast Cancer (%)	18.59	19.28	0.8599	21.21	0.2756

*Values are means (SD) or percentages and are standardized to the age distribution of the study population.

+P-values generated from linear and logistic generalized estimating equation models using the working correlation matrix examining sexual orientation group differences with heterosexual as the referent group, controlling for age, race/ethnicity, region of residence, and household income.

§Among the subset of women (n=63,680) who reported at least one birth.

¥Calculated based on BMI beginning at age 18 years.

Table 3

Predicted mean annual breast cancer incidence rate (IR) per 100,000 person-years, incidence rate ratios (IRR) relative to heterosexual referent group, and 95% confidence intervals (CI), by sexual orientation and age group in a U.S. cohort of premenopausal women (N = 87,392)

	Sexual Orientation						
	Heterosexual	Lesbian	Lesbian vs. Heterosexual		Bisexual	Bisexual vs. Heterosexual	
	Mean IR* (95% CI)	Mean IR* (95% CI)	P-value+	IRR (95% CI)§	Mean IR* (95% CI)	P-value+	IRR (95% CI)§
All Ages							
25–58 years	122.55 (122.40, 122.70)	131.61 (129.68, 133.54)	<.0001	1.0635 (1.06, 1.06)	131.72 (128.86, 134.58)	<.0001	1.10 (1.10, 1.10)
Age Groups							
25–34 years	45.83 (45.75, 45.92)	50.65 (49.35, 51.95)	<0.0001	1.08 (1.08, 1.08)	50.38 (48.55, 52.22)	<0.001	1.12 (1.12, 1.12)
35–44 years	105.63 (105.50, 105.75)	113.83 (112.26, 115.41)	<0.0001	1.06 (1.06, 1.06)	113.09 (110.78, 115.40)	<0.0001	1.09 (1.09, 1.09)
45–58 years	209.71 (209.36, 210.07)	223.29 (218.97, 227.60)	<0.0001	1.07 (1.07, 1.07)	225.27 (218.87, 231.67)	<0.001	1.10 (1.10, 1.10)

*Predicted annual breast cancer incidence rates per 100,000 person-years estimated with Rosner-Colditz breast cancer risk prediction model adjusted for age, race and income.

+P-value for test of difference from heterosexual comparison group.

§Incidence rate ratio (IRR) and 95% confidence interval (CI) for comparison to heterosexual referent group adjusted for age, race and income.