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Application of the Rosner-Wei Risk-Prediction Model to Estimate Sexual Orientation Patterns in Colon Cancer Risk in a Prospective Cohort of U.S. Women

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Abstract

Purpose—We examined whether lesbian and bisexual women may be at greater risk of colon cancer (CC) than heterosexual women.

Methods—Working with a large cohort of U.S. women ages 25-64 years, we analyzed 20 years of prospective data to estimate CC incidence, based on known risk factors by applying the Rosner-Wei CC risk-prediction model. Comparing to heterosexual women, we calculated for lesbian and bisexual women the predicted one-year incidence rate (IR) per 100,000 person-years and estimated incidence rate ratios (IRR) and 95% confidence intervals (CI), based on each woman's comprehensive risk factor profile.

Results—Analyses included 1,373,817 person-years of data from 66,257 women. For each sexual orientation group, mean predicted one-year CC IR per 100,000 person-years was slightly over 12 cases for each of the sexual orientation groups. After controlling for confounders in fully adjusted models and compared to heterosexuals, no significant differences in IRR were observed for lesbians (IRR 1.01; 95% CI 0.99, 1.04) or bisexuals (IRR 1.01; 95% CI 0.98, 1.04).

Conclusions—CC risk is similar across all sexual orientation subgroups, with all groups comparably affected. Health professionals must ensure that prevention, screening, and treatment programs are adequately reaching each of these communities.

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Keywords

colon cancer; risk model; sexual orientation; bisexual; lesbian

Introduction

Colon cancer (CC) is the third most commonly diagnosed cancer in U.S. women (1). In 2013, an estimated 69,140 women will be diagnosed with CC and another 24,530 will die of the disease (1). Prior epidemiologic research documenting higher prevalence of risk factors for CC, such as obesity, smoking, physical inactivity, among lesbian and bisexual women suggests these women may be at elevated lifetime risk for the disease compared to heterosexual women (2-11). Very little research exists, however, examining whether there are sexual orientation group disparities in CC incidence. The dearth of research likely results from a combination of factors. First, the U.S. National Cancer Institute's Surveillance Epidemiology and End Results (SEER) registry does not include information on sexual orientation (5, 12). This registry is an invaluable resource for identifying disparities in incidence and survival by sex, age, race/ethnicity, region of residence, and socioeconomic status and for monitoring the outcomes of efforts to mitigate disparities. Yet, without the inclusion of data on sexual orientation, the potential of the registry to contribute to our understanding of the relationship between sexual orientation and CC or any cancer is yet to be realized (5, 12, 13). Second, few epidemiologic studies are large enough in terms of sample size to compare cancer incidence across sexual orientation subpopulations (13).

In the absence of sexual orientation data in SEER and many large cohort studies, researchers have employed alternative methods to assess CC in sexual minority populations. Boehmer et al. compared self-reported CC history between lesbian and heterosexual women ages 18 to 65 years using data from the California Health Interview Survey, pooling data across three waves from 2001 to 2005 (14). They did not find a significant difference in self- reported history of colon cancer between lesbians and heterosexual women. In a subsequent study, Boehmer and colleagues obtained colorectal cancer incidence and mortality rates in 215 counties across the country from the SEER registry and then analyzed those data along with U.S. Census 2000 data on county-level density of female same-sex partnered households, which they proposed as a proxy for sexual minority female population density. Using an ecological analysis approach, the authors estimated that a county's colorectal cancer incidence rate was elevated by 6% for each one percent higher density of sexual minority women (15).

Another method used to estimate sexual orientation group differences in cancer incidence rates in the absence of SEER data is incidence modeling based on unique risk factor profiles for each sexual orientation subgroup. This approach is particularly advantageous for estimating incidence of rare diseases in small populations because these models can generate estimates from samples smaller than what would be required to accrue sufficient numbers of actual cases of a rare disease to allow tests of group differences in observed (as opposed to predicted) incidence. Risk-prediction modeling has been used specifically with breast cancer, where both the Gail model(16) and the Rosner-Colditz risk-prediction model (17-19)

have been applied to samples of lesbian, bisexual, and heterosexual women, most finding evidence of higher predicted incidence of breast cancer in sexual minority relative to heterosexual women (13, 20-22). A model similar to the Rosner-Colditz breast cancer risk-prediction model has been developed to estimate incidence rates for CC. The Rosner-Wei CC risk-prediction model is risk-prediction model founded on the assumption that CC incidence is proportional to the number of colon cell divisions accrued through the life course up to a defined age (23). Beginning with risk factors previously identified as causally related to CC, the log of the rate of cell divisions is treated in the model as a linear function of these risk factors. Importantly, the model takes into account the differential effects that various risk factors may have depending on a woman's age or period of her life. Beta coefficients assigned to each risk factor included in the model quantify the effect of that risk factor at a specified age or life period. Risk factor model parameters can be used to estimate relative risks for specific risk factor profiles and years of exposure (23).

With respect to the factors known to influence CC risk -- such as a lack of physical activity, high intake of red or processed meat, low folate intake, cigarette smoking, aspirin use, and postmenopausal hormone use -- the nonlinear log-incidence model allows for better accounting for complex interrelationships regarding colon carcinogenesis (23). An improvement over a standard logistic regression model, the Rosner-Wei log-incidence model allow for more sophisticated quantification of time-varying effects and interactive properties of risk factors known to affect CC risk. Seeking to take advantage of the strengths of the Rosner-Wei risk-prediction model, we applied the model in a large, national cohort of U.S. women ages 25-64 years old with the aim of estimating sexual orientation group-specific CC incidence rates. We hypothesized that lesbian and bisexual women would have higher predicted incidence of CC compared to heterosexual women.

Methods

Study sample

The Nurses' Health Study (NHS) II cohort was first assembled in 1989, when a baseline questionnaire was sent to approximately 520,000 registered nurses from across the United States, targeting those living in the 14 most populous states; this recruitment effort led to the enrollment of 116,430 women into the cohort (24). Informed consent for study participation was inferred from the completion and return of the baseline questionnaire. Questionnaires assessing disease risk factors and incidence have been completed by the cohort every two years since baseline, when participants were ages 25-42 years old. The racial/ethnic composition of the cohort is 94% white, 2% African-American, 2% Latina, and 2% Asian. Institutional review board approval has been received from Brigham and Women's Hospital and the Harvard School of Public Health.

Measures

In the 1995 wave of NHSII data collection, sexual orientation identity was assessed with the following item (6): "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. The present analyses included three groups: heterosexual, lesbian/gay/homosexual (referred to as "lesbian" henceforth), and bisexual women.

Every NHSII questionnaire assesses whether CC has been diagnosed since the previous questionnaire cycle. In addition, NHSII research staff regularly review the National Death Index to assess whether participants who did not respond to a questionnaires may have died. Medical record review was used to confirm all reports of cancer diagnosis with consent of participants or, in the case of participant death, with consent of a family member (25). Diagnosis of any cancer (with the exception of non-melanoma skin cancer) prompted exclusion from the current analyses from that point on, though risk factor data from the period prior to diagnosis were included in analyses. Each questionnaire, excluding 1989, participants are also asked if they have received colorectal screening, specifically a colonoscopy or sigmoidoscopy in the past two years and for what reason (i.e., routine screening or follow-up due to abnormal finding). Based on a report of having been screened, we assigned each participant a screening "coverage" value of four years (or two data collection cycles) beginning at her age at screening to approximate the recommended interval for routine colorectal screening. Each participant's total years of screening "coverage" was then summed and assigned as her value for the colorectal screening variable (23).

In four questionnaire cycles (1989, 1997, 2001, 2005, and 2009), participants were asked to report any family history of CC. At baseline in 1989, current height and weight were assessed in addition to retrospective assessment of weight at age 18 years. Weight has also been assessed at every data collection cycle since baseline. Self-reported current weight and weight at age 18 have been found to be valid measures (26, 27). Height and weight data were used to calculate body mass index (BMI; kg/m^2) beginning at age 18 years and then at each questionnaire cycle. Information about physical activity has been collected nearly every questionnaire cycle, excluding 1999, 2003, and 2009. Three questionnaire cycles included an item asking participants to indicate how many times per week they engage in physical activity long enough to induce heavy perspiration, and two questionnaires include items asking participants to indicate their past physical activity. In 1997 a series of detailed items asked about physical activity and sedentary behaviors starting at grade 7 though age 34 years. Similarly, nearly every questionnaire collecting information on physical activity included a series of items asking participants to indicate how many times per week they engaged in a particular sport or activity such as tennis or aerobic exercise as well as how much sedentary time they spend sitting at work, home or in the car. These questions allow for the calculation of total metabolic, or MET, hours per week, derived from the type and duration of activities reported.

We assessed postmenopausal hormone (PMH) use at baseline and at each subsequent questionnaire cycle. Women are asked to indicate what type and dose of PMH they use, either conjugated estrogen or progestin. Aspirin use has been collected nearly every questionnaire cycle, querying women about frequency, dose, and duration of aspirin use. Beginning in 1991, a previously validated (28, 29), semi-quantitative food-frequency questionnaire (FFQ) was included with the general questionnaire in alternating waves to determine the long-term average diet of the cohort. Dietary assessment includes intake of

folate (mcg/day), processed meat (servings/day), and red meat (servings/day). Information about smoking has been collected each questionnaire cycle, querying women about frequency, amount smoked, and quit attempts.

Race/ethnicity was assessed at baseline by asking women to select the best description for themselves from a list of categories, which were then coded as follows: white, African-American, Latina, Asian-American, multiracial, and missing (30). In 2001, women were asked to report their annual household income, which was then coded into four groups: Less than $50,000; $50,000 to less than $75,000; $75,000 to less than $100,000; and $100,000 or greater. Four regions of residence, including Northeast, South, Midwest, and West, were assigned based on information gathered from participants and updated each questionnaire cycle.

Statistical Analyses

We included participants who provided data from baseline (1989) through the 2009 cycle of data collection. Our analytic sample included women ages 25-64 years old throughout follow-up. The upper limit of age 64 years was used to ensure our analyses had sufficient sample sizes of lesbian and bisexual women at the older ages. As repeated measures information was collected for most variables, those included in models were either updated or cumulatively updated. Carry-forward methods or cumulatively updated averages, as appropriate, were used in some cases when covariates were not available on a wave (31). Our analyses included 66,257 (56.9% of the original cohort of 116,430) participants providing 1,373,817 person-years of data.

Based on the Rosner-Wei CC risk-prediction model (23), we conducted a series of analytic steps. First, we compared CC risk factors in lesbian and bisexual women to those in heterosexual women using linear and logistic generalized estimating equation models, controlling for age, race/ethnicity, region of residence, and household income. Next, we estimated predicted one-year CC incidence rates (IR) per 100,000 person-years, using the parameters in and methods of the Rosner-Wei model, then examined differences in predicted IRs by sexual orientation group, controlling for age. We estimated the predicted one-year CC IR by using risk factor data reported by each participant at each questionnaire wave. As a result, a predicted one-year IRs were calculated based on the updated information at each questionnaire cycle (e.g., hours of physical activity per week) or by carrying forward information when appropriate (e.g., BMI at age 18 years). Finally, comparing lesbian and bisexual women to heterosexual women overall and within each age strata (25-34 years, 35-44 years, 45-54 years, and 55-64 years), we also calculated CC incidence rate ratios (IRR) and 95% confidence intervals (CI), controlling for age. With the working correlation matrix, we used generalized estimating equation (GEE) methods to account for correlated data arising from repeated measures (32).

Results

Table 1 presents sociodemographic characteristics of the 66,257 NHSII participants contributing data to our analyses. The cohort, made up of women living in all four regions of the country, included approximately 1% lesbian and bisexual women and 6% women of

color. More than 35% of women reported a 2001 annual household income of $100,000 or greater. Differences by sexual orientation were observed, where, compared to heterosexual women, lesbian and bisexual women reported higher rates of living in the West and lower annual household income. During the follow-up period, 0.25% (166 cases) of heterosexual women but no lesbian or bisexual women were diagnosed with CC (not in table).

CC risk factors included in the Rosner-Wei model are presented in Table 2 along with the means and frequencies for each sexual orientation group. In terms of factors that increase CC risk, compared to heterosexual women, lesbians were older, and both lesbian and bisexual women were taller, had greater smoking and higher BMI. On the other hand, in terms of protective factors, compared to heterosexual women, both lesbian and bisexual women reported consuming significantly less red and processed meat, and lesbians reported more physical activity.

Predicted CC incident cases are shown in Table 3 for each sexual orientation group and for all ages and within age strata. For women of all ages in each sexual orientation group, mean predicted one-year CC IRs per 100,000 person-years were as follows: heterosexual 12.23, lesbian 12.42, and bisexual 12.33 cases per 100,000 person-years. After controlling for age and compared to heterosexuals, no significant differences in IRR were observed for lesbians (IRR 1.01; 95% CI 0.99, 1.04) or bisexuals (IRR 1.01; 95% CI 0.98, 1.04). In analyses by age strata, no predicted IRs were statistically significantly different from those of same-age heterosexual women.

Discussion

It has been known for some time that lesbian and bisexual women experience higher rates than heterosexual women of some important CC risk factors, including smoking and obesity. Yet little research has been conducted to investigate whether sexual minority women are disproportionately affected by this cancer. Our study adds new information on predicted incidence to a small body of research focused on understanding the experiences of sexual minority women in terms of CC risk factors, incidence, mortality, and survivorship (14, 15). In the NHSII cohort, one of the largest and longest running prospective cohort studies of women’s health in the world, we found no evidence of elevated predicted CC risk in lesbian or bisexual women compared to heterosexual women ages 25 to 64 years old. Applying the Rosner-Wei risk-prediction model, a comprehensive model that accounts for time-varying exposures to predict CC risk, we estimated that lesbian, bisexual, and heterosexual women had a one-year IR of approximately slightly over 12 cases per 100,000 person-years. By comparison, for U.S. women under the age of 65 years, the National Cancer Institute estimates the colon cancer incidence rate to be 10.3 cases per 100,000 person-years for women of all race/ethnicities combined and 9.7 cases per 100,000 person-years for white women (33).

Two previous studies examining the relationship between sexual orientation and CC risk in women had conflicting results. Boehmer et al. analyzed ecological data at the county level linking SEER incidence data for colorectal cancer and U.S. Census data on density of female same-sex households (15). Based on their findings, they estimated the colorectal

cancer incidence rate would be expected to increase by 6% for each one percent higher density of sexual minority women living in a county. In another study by Boehmer et al., the research team analyzed individual-level data from women ages 18-65 years participating in the California Health Interview Survey and did not find a significant difference in self-reported history of CC (14). Our study, which was similarly based on individual-level data, did not find a statistically significant difference in CC risk across sexual orientation groups. It is not clear why Boehmer et al.'s ecological study (15) estimated higher risk associated with female same-sex households, but studies based on detailed, individual-level risk exposure measures over many years are likely to provide more precise estimates of risk than studies based on ecological data. Our study extends the current literature in several important ways. Our estimates are based on 20 years of prospectively collected individual-level, repeated-measures data from one of the largest ongoing longitudinal cohorts of women in the world. In addition, our estimates are derived from the Rosner-Wei risk-prediction model, which is a comprehensive model that incorporates the repeated measures available in the NHS2 data (23).

Our findings suggest that each year up through age 64 years and compared to heterosexual women, lesbian and bisexual women may not have elevated risk of CC. These findings were not consistent with our hypotheses of higher risk in sexual minorities. Our findings suggest that CC is a serious health concern for all women, regardless of sexual orientation. Programs designed to prevent, screen, or treat the disease must be appropriate and sensitive to the needs of women of diverse sexual orientations. Routine screening for colon cancer is highly effective in preventing the disease, yet in a prior study, our research group found colorectal screening to be universally low in all sexual orientation subgroups, with fewer than half in each group meeting screening recommendations.(34) The findings of this prior study combined with our current study underscore the need for improved CC prevention and control efforts appropriate for all sexual orientation communities.

Limitations of our study include the use of self-report data and nonrepresentativeness of the cohort. The vast majority of participants were white race/ethnicity and all were professional nurses at the time of recruitment, thus narrowing the range of socioeconomic position compared to that of the general U.S. population. In addition, for our analyses, the upper age limit for inclusion was 64 years old. Risk of CC increases substantially with age, but given the participant age range of 25-42 years old at baseline in 1989, the cohort had not yet accrued enough observations among older women for us to conduct meaningful analyses related to CC beyond age 64 years. Lastly, a validation study of the Rosner-Wei model is ongoing, so results from that study are not yet available. External validation of the parameters in the model will provide additional confidence in the model's general predictive ability. Future research should investigate whether there may be sexual orientation-related disparities in CC among women ages 65 years and older.

CC is among the most common cancers affecting adults in the United States, taking the lives of almost 25,000 women every year (1). Health professionals must ensure that prevention, screening, and treatment efforts are adequately reaching sexual minority as well as heterosexual communities. Furthermore, tracking cancer incidence and mortality in all sexual orientation groups is vital. As more health systems across the country add sexual

orientation to their data collection protocols, efforts to monitor cancer incidence and mortality will be substantially improved by the addition of patient sexual orientation data in the National Cancer Institute's SEER cancer registry.

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Table 1

Sociodemographic characteristics of women in the Nurses' Health Study II ages 25-42 years at baseline in 1989 (N = 66,257)[a]

		Sexual Orientation				
Sociodemographics	**N**	**Heterosexual (N = 65469)**	**Lesbian (N = 545)**	**P-value[b]**	**Bisexual (N = 243)**	**P-value[c]**
Race/Ethnicity				0.05		0.76
African-American, %	896	1.38	0.55		1.25	
Latina, %	998	1.53	1.29		2.08	
Asian, %	1,074	1.65	0.74		0.83	
White (non-Latina), %	61,269	93.70	96.69		94.61	
Other Ancestry, %	1,133	1.74	0.74		1.25	
Region of Residence				<.001		<.001
East, %	16,037	24.24	23.90		28.40	
Midwest, %	22,809	34.65	21.14		22.63	
South, %	14,992	22.69	22.61		20.17	
West, %	12,278	18.42	32.35		28.81	
Household Income				<.001		<.001
<$50,000/year, %	7,559	15.60	21.83		25.39	
$50-75,000/year, %	13,085	27.14	29.18		29.02	
$75-100,000/year, %	10,256	21.35	17.60		17.10	
$100,000/year, %	17,267	35.92	31.40		28.50	

[a] Values are percentages; percentages and Ns calculated out of nonmissing; values of polytomous variables may not sum to 100% due to rounding.

[b] P-value from χ^2 test comparing lesbians to heterosexuals.

[c] P-value from χ^2 test comparing bisexuals to heterosexuals.

Table 2

Age-standardized risk factors, by sexual orientation, included in Rosner-Wei risk-prediction model to estimate disparities in colon cancer risk in a U.S. cohort of women (total person-years = 1,373,817)[a]

	Sexual Orientation				
Colon Cancer Risk Factors	**Heterosexual (person-years = 1,357,815**	**Lesbian (person-years = 11,157)**	**P-Value [b]**	**Bisexual (person-years = 4,845)**	**P-Value [b]**
Age (years)	44.14	44.89	0.0495	44.74	0.3290
Family History (%)	7.6	8.9	0.1126	7.8	0.7682
Red and Processed Meat (Serving per day)	0.30	0.23	<.0001	0.24	<.0001
Smoking (Pack years)	4.45	8.11	<.0001	7.00	0.0002
Current Postmenopausal Hormone (PMH) Use (%)	13.2	12.9	0.4362	13.6	0.8310
Past PMH Use (%)	28.9	27.9	0. 6796	29.5	0.6836
Aspirin (Tablets per week)	0.84	0.93	0.0840	0.94	0.1378
Physical Activity (MET hours per week)	19.85	22.79	0.0006	21.35	0.1623
BMI (kg/m^2)[c]	23.79	25.18	<.0001	24.49	0.0205
Height (Inches)	64.91	65.19	0.0484	65.24	0.0442
Folate (Energy-adjusted antilog g per day)	517	525	0.0837	523	0.7275
Colorectal Screening (Years of coverage after age 30)	1.44	1.55	0.0885	1.51	0.5383

[a] All variables except age are standardized to the age distribution of the heterosexual study population.

[b] P-values generated from linear and logistic generalized estimating equation models using the exchangeable 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; P-value for the age variable from models controlling race/ethnicity, region of residence, and household income.

[c] Calculated based on BMI beginning at age 18 years.

Table 3

Predicted mean annual colon 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 women

	Sexual Orientation						
	Heterosexual	Lesbian	Lesbian vs. Heterosexual		Bisexual	Bisexual vs. Heterosexual	
	Mean IR[a] (95% CI)	Mean IR[a] (95% CI)	P-value[b]	IRR (95% CI)[c]	Mean IR[a] (95% CI)	P-value[b]	IRR (95% CI)[c]
All Ages							
25-64 years	12.23 (12.21, 12.26)	12.42 (12.15, 12.69)	0.186	1.01 (0.99, 1.04)	12.33 (11.94, 12.73)	0.641	1.01 (0.98, 1.04)
Age Groups							
25-34 years	4.70 (4.70, 4.71)	4.77 (4.67, 4.87)	0.190	1.01 (0.99, 1.04)	4.74 (4.62, 4.87)	0.510	1.01 (0.98, 1.04)
35-44 years	9.22 (9.21, 9.24)	9.39 (9.21, 9.57)	0.064	1.02 (1.00, 1.04)	9.28 (9.05, 9.51)	0.636	1.01 (0.98, 1.03)
45-54 years	17.03 (16.99, 17.07)	17.32 (16.84, 17.82)	0.238	1.02 (0.99, 1.05)	17.06 (16.40, 17.76)	0.927	1.00 (0.96, 1.04)
55-64 years	32.33 (32.19, 32.47)	32.15 (30.73, 33.63)	0.806	0.99 (0.95, 1.04)	32.40 (29.89, 35.12)	0.957	1.00 (0.92, 1.09)

[a] Predicted annual colon cancer incidence rates per 100,000 person-years estimated with Rosner-Wei colon cancer risk prediction model adjusted for age, using linear generalized estimating equation models using the exchangeable working correlation matrix, weighted using 1/predicted incidence.

[b] P-value for test of difference from heterosexual comparison group.

[c] Incidence rate ratio (IRR) and 95% confidence interval (CI) for comparison to heterosexual referent group adjusted for age.