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Original Contribution

Proportion of Invasive Breast Cancer Attributable to Risk Factors Modifiable after Menopause

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A number of breast cancer risk factors are modifiable later in life, yet the combined impact of the population changes in these risk factors on breast cancer incidence is not known to have been evaluated. The population attributable risk (PAR) associated with individual risk factors and the summary PAR for sets of modifiable and nonmodifiable risk factors were estimated by using data on 3,499 invasive breast cancer cases and 4,213 controls from a population-based study in Wisconsin, Massachusetts, and New Hampshire, conducted from 1997 to 2001. The summary PAR for factors modifiable after menopause, including current postmenopausal hormone use, recent alcohol consumption, adult weight gain, and recent recreational physical activity, was 40.7%. Of the individual modifiable factors, the highest PARs were observed for weight gain (21.3%) and recreational physical activity (15.7%), which together showed a summary PAR of 33.6%. The summary PAR for factors not modifiable after menopause, including family history of breast cancer, personal history of benign breast disease, height at age 25 years, age at menarche, age at menopause, age at first birth, and parity, was 57.3%. These findings suggest that a substantial fraction of postmenopausal breast cancer may be avoided by purposeful changes in lifestyle later in life.

alcohol drinking; breast neoplasms; case-control studies; exercise; hormone replacement therapy; risk factors; weight gain

Abbreviation: PAR, population attributable risk.

Many prominent risk factors for breast cancer are not amenable to modification, particularly later in life. Included are reproductive and menstrual factors (e.g., age at menarche, age at first birth) and family history of breast cancer. However, over the past 10 years, our understanding of modifiable breast cancer risk factors has improved, particularly with regard to postmenopausal hormone use, alcohol consumption, weight gain, and physical activity (1). Few studies have evaluated the potential impact on breast cancer incidence of population changes in these modifiable risk factors.

The population attributable risk (PAR) refers to the proportion of all cases that would not have occurred if exposure to a causal factor was removed from the population (2). When calculated for a set of multiple risk factors, it is referred to as a summary PAR. Depending on the factors examined and the cutpoints used for ''exposed'' categories, summary PARs for various sets of breast cancer risk factors

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have ranged from 15 percent to 55 percent (3–8). Most previous studies have focused on reproductive and menstrual risk factors and family history of breast cancer (3–7). Relatively few data are available on the PAR associated with the totality of established modifiable risk factors (8); such an analysis would help inform the potential for public health interventions to reduce breast cancer incidence.

For certain modifiable risk factors, exposure cannot be completely altered later in life. For instance, postmenopausal hormone users cannot revert to ''never user'' status but can become only ''former users.'' Thus, two aspects of the PAR for modifiable factors are of interest. The first is the reduction in incidence that could be accomplished among women given their past exposure, for example, cessation of hormone use. This is of particular public health interest because it represents what might be accomplished immediately by lifestyle changes among women. The second is the reduction in incidence that would be accomplished if exposure to the risk factor had never occurred. For factors such as hormone use, this may be strictly theoretical (e.g., a ''current user'' becoming a ''never user'') but may also be useful in representing what is possible for future generations of women.

We investigated invasive breast cancer risk among postmenopausal women in a large, collaborative case-control study conducted between 1997 and 2001 in Wisconsin, Massachusetts, and New Hampshire (9). We examined the PAR associated with individual risk factors and the summary PAR associated with sets of factors modifiable after menopause versus those nonmodifiable after menopause.

MATERIALS AND METHODS

This study was performed with data from the Collaborative Breast Cancer Study (9) according to protocols approved by the institutional review boards at the University of Wisconsin (Madison, Wisconsin), Harvard University (Boston, Massachusetts), and Dartmouth Medical School (Lebanon, New Hampshire).

Study population

The study population has previously been described (9). Briefly, eligible cases were English-speaking female residents of Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire, aged 20–69 years, with a new diagnosis of invasive breast cancer reported to each state's mandatory cancer registry during 1996–2000. Eligibility was limited to cases with known dates of diagnosis and, for comparability with controls, listed telephone numbers and a self-reported driver's license (if <65 years of age). Of the 8,066 eligible women with invasive cases of disease, 6,429 (80 percent) participated.

Controls were randomly selected in each state from the community by using two sampling frames: those less than 65 years of age were selected from lists of licensed drivers, and those 65–69 years of age were selected from a roster of Medicare beneficiaries compiled by the Centers for Medicare & Medicaid Services. Controls were selected at random within 5-year age strata to yield an age distribution similar to that for the cases enrolled in each state, and they were required to have no personal history of breast cancer, to have a listed telephone number, and, if less than 65 years of age, to have a self-reported driver's license. Of the 10,161 eligible controls, 7,683 (76 percent) participated.

Data collection

In telephone interviews conducted between February 1997 and May 2001, study participants reported their reproductive and menstrual history, height and weight, exogenous hormone use, personal and family medical history, alcohol consumption, recreational physical activity, and demographic factors. Women were asked whether a physician had ever told them that they had benign breast disease or fibrocystic breasts. For postmenopausal hormone use, women were asked to report all episodes of use of oral, injectable, and transdermal estrogen and/or progesterone for at least 3 months of total cumulative duration. Regarding alcohol consumption, participants were asked to report their typical consumption of beer, wine, and liquor-containing drinks during the past year. Lifetime history of recreational physical activity was assessed with a format of questions previously described (9), in which participation in various activities between age 14 years and a year prior to the reference date was ascertained, including jogging/running, bicycling, calisthenics/aerobics/dance, racquet sports, swimming, and walking/hiking for exercise. Each subject reported her age when the activity was started and stopped as well as the number of months per year and the number of hours per week that the activity was undertaken.

Statistical analysis

For each case, a reference date was defined as the registry-supplied date of breast cancer diagnosis. For comparability, the controls interviewed contemporaneously with cases were assigned, prior to interview, an individual reference date based on the distribution of days from diagnosis to interview for the cases already interviewed.

All analyses were restricted to postmenopausal women, yielding 3,499 cases and 4,213 controls (54.4 percent and 54.8 percent of all participants, respectively). A woman was defined as postmenopausal if she reported a natural menopause (no menstrual periods for at least 6 months) before the reference date. Women who reported taking hormone replacement therapy and still having periods, and women who reported hysterectomy alone, were classified as postmenopausal if their reference ages were in the highest decile for age at natural menopause in the control group ($\geq$54 years of age for current smokers and $\geq$56 years of age for nonsmokers); age at menopause was defined as unknown for these women. Postmenopausal hormone use was categorized as never, former, or current, with current users classified according to type of hormone use: exclusively estrogen only, estrogen and progestin combined, or other (e.g., users of both types of regimens, progestin only, Estratest (Solvay Pharmaceuticals, Marietta, Georgia)). A woman was considered to have a first-degree family history of breast cancer if

she reported that her mother, sister, or daughter had been diagnosed with breast cancer. Recent recreational physical activity was computed by dividing the total number of hours of exercise reported for the period between 6 years and 1 year prior to the subject's reference date by the number of weeks between these two dates.

All analyses were performed by using SAS Statistical Software (version 9; SAS Institute, Inc., Cary, North Carolina). Multivariable logistic regression models were used to estimate odds ratios and 95 percent confidence intervals associated with each risk factor. The models included the following variables selected a priori: age, US state of residence, first-degree family history of breast cancer, personal history of benign breast disease, height at age 25 years, age at menarche, age at menopause, age at first full-term pregnancy, parity, oral contraceptive use, lactation duration, postmenopausal hormone use, alcohol consumption, weight at age 18 years, weight change from age 18 years until 1 year prior to the reference date, recent recreational physical activity, and number of screening mammograms per year in the 5 years prior to the reference date. All variables were parameterized as shown in tables 1 and 2, with missing data categorized as unknown.

The PAR represents the proportion of cases that would be eliminated if the entire population moved into a specified low-risk category of an individual factor or combination of factors while the other variables were held constant. In the PAR calculations, the reference categories shown in tables 1 and 2 served as the specified low-risk category. In the PAR calculation for postmenopausal hormone use, we assumed no change in risk for ''never'' users (i.e., the PAR represents exclusively the effect of converting ''current'' users to ''former'' users). For age at first full-term pregnancy, nulliparous women were assumed to have no change in risk (i.e., the PAR represents exclusively the effect of lowering the age at first pregnancy to <20 years for all parous women). For weight gain since age 18 years, no change in risk was assumed for women who lost more than 5 kg (i.e., the PAR represents the effect of shifting all women who gained more than 5 kg to the stable-weight reference category). For each variable, women in the missing category were assumed to have no change in risk for that variable's PAR calculation.

A number of methods have been developed to calculate the PAR associated with specific risk factors (10–12). The generalized regression-based approach described by Bruzzi et al. (4) accounts for possible confounding, effect modification, and multicategory exposure levels. PARs were computed by using this method, with the following formula: $\mathrm{PAR} = 1 - \sum_j p_j/\mathrm{RR}_j$, where p_j is the proportion of cases in stratum j of the risk factor distribution and RR_j is the multivariable-adjusted relative risk associated with that stratum of the risk factor(s). Odds ratios produced by the multivariable logistic regression were used as estimates of the relative risks. An individual PAR was calculated for each risk factor, and summary PARs were calculated for various sets of factors. A bootstrapping method was used to obtain 95 percent confidence intervals for the PAR estimates (7, 13). Briefly, a SAS macro was created to sample, with replacement, 3,499 cases and 4,213 controls from the original data set, and the PAR of interest was calculated. This procedure was repeated 1,000 times, and the 2.5th and 97.5th percentiles of the PAR estimates formed an approximate 95 percent confidence interval around the original estimate.

RESULTS

The cases consisted of 2,321 (66.3 percent) localized, 822 (23.5 percent) regional, 56 (1.6 percent) distant, and 300 (8.6 percent) unknown-stage invasive breast cancers. The average age of the breast cancer cases at diagnosis was 60.7 (standard deviation, 5.9) years, whereas the average age of controls at their reference date was 60.4 (standard deviation, 6.0) years. Cases were more likely than controls to have had at least one screening mammogram per year over the 5 years preceding their reference date (65.4 percent for cases vs. 57.0 percent for controls). Overall, study subjects were 95.6 percent non-Hispanic White.

As expected, a first-degree family history of breast cancer, a personal history of benign breast disease, and height at age 25 years were each positively associated with breast cancer risk (table 1). Similarly, women who were younger at menarche, were older at menopause, were older at their first full-term pregnancy, and had fewer children were at increased risk of developing breast cancer. Duration of oral contraceptive use and breastfeeding history were not associated with breast cancer risk.

Postmenopausal hormone use was associated with breast cancer risk (table 2). Compared with the risk for former users, the increased risk for current users was essentially restricted to women who used combined estrogen and progestin formulations. Alcohol consumption, weight gain since age 18 years, and physical inactivity were each positively associated with breast cancer risk.

The PARs associated with various individual risk factors and combinations of risk factors are shown in table 3. For the set of factors considered nonmodifiable after menopause, the summary PAR was 57.3 percent. Among these factors, the largest individual PARs were observed for age at menarche (18.8 percent), age at menopause (13.7 percent), and parity (13.3 percent). Combined with age at first full-term pregnancy, these four reproductive and menstrual factors yielded a summary PAR of 42.2 percent. Moderate PARs were observed for a first-degree family history of breast cancer (8.5 percent), a personal history of benign breast disease (9.7 percent), and height at age 25 years (11.0 percent).

For the set of factors considered modifiable after menopause, the summary PAR was 40.7 percent. The largest PARs were observed for weight gain since age 18 years (21.3 percent) and recent recreational physical activity (15.7 percent), although the 95 percent confidence interval for physical activity did not exclude zero. For these two factors combined, weight gain and physical activity, the summary PAR was 33.6 percent (95 percent confidence interval: 15.3, 48.8).

The PAR reported in table 3 for postmenopausal hormone use (4.6 percent) represents the effect of converting current users to former users. The PAR for postmenopausal hormone use if both former and current users were able to become never users (e.g., in some future population) was 8.5 percent (95 percent confidence interval: 4.0, 13.3).

TABLE 1. Odds ratios and 95% confidence intervals for factors not modifiable after menopause in relation to postmenopausal invasive breast cancer risk, Wisconsin, Massachusetts, and New Hampshire, 1997–2001

Factor	No. of controls	%*	No. of cases	%*	OR†,‡	95% CI†	OR§	95% CI
First-degree family history of breast cancer								
No	3,500	83.1	2,636	75.3	1	Reference	1	Reference
Yes	585	13.9	746	21.3	1.67	1.49, 1.89	1.66	1.46, 1.88
Personal history of benign breast disease								
No	3,318	78.8	2,432	69.5	1	Reference	1	Reference
Yes	832	19.8	986	28.2	1.64	1.48, 1.83	1.53	1.36, 1.71
Height at age 25 years (m)								
<1.60	1,106	26.3	797	22.8	1	Reference	1	Reference
1.60–1.62	1,083	25.7	890	25.4	1.11	0.98, 1.26	1.11	0.98, 1.27
1.63–1.67	1,129	26.8	955	27.3	1.15	1.02, 1.31	1.14	1.00, 1.31
≥1.68	848	20.1	823	23.5	1.32	1.15, 1.50	1.27	1.09, 1.48
Age at menarche (years)								
<12	863	20.5	770	22.0	1.36	1.15, 1.60	1.37	1.15, 1.63
12	924	21.9	822	23.5	1.35	1.14, 1.59	1.33	1.12, 1.58
13–14	1,820	43.2	1,480	42.3	1.22	1.05, 1.41	1.20	1.02, 1.40
≥15	531	12.6	355	10.2	1	Reference	1	Reference
Age at menopause (years)								
<45	1,176	27.9	780	22.3	1	Reference	1	Reference
45–49	966	22.9	783	22.4	1.24	1.09, 1.41	1.22	1.06, 1.40
50–54	1,279	30.4	1,124	32.1	1.32	1.17, 1.50	1.25	1.09, 1.42
≥55	415	9.9	409	11.7	1.47	1.24, 1.73	1.40	1.18, 1.68
Unknown	377	9.0	403	11.5	1.58	1.34, 1.87	1.39	1.15, 1.67
Age at first full-term pregnancy (years)¶								
<20	827	21.8	597	19.5	1	Reference	1	Reference
20–24	2,010	53.0	1,568	51.3	1.10	0.97, 1.24	1.02	0.89, 1.16
25–29	740	19.5	654	21.4	1.28	1.10, 1.49	1.15	0.98, 1.36
≥30	202	5.3	236	7.7	1.69	1.36, 2.10	1.42	1.11, 1.80
Parity								
0–1	756	17.9	767	21.9	1.54	1.35, 1.76	1.35	1.12, 1.65
2	948	22.5	854	24.4	1.36	1.20, 1.54	1.26	1.10, 1.44
3	1,020	24.2	810	23.2	1.17	1.04, 1.32	1.13	0.99, 1.28
≥4	1,476	35.0	1,051	30.0	1	Reference	1	Reference
Oral contraceptive use (months)								
0	2,512	59.6	2,031	58.1	1	Reference	1	Reference
1–36	662	15.7	549	15.7	1.04	0.91, 1.19	1.04	0.91, 1.19
>36	979	23.2	867	24.8	1.10	0.98, 1.23	1.09	0.97, 1.23
Lactation duration (months)¶								
0	2,330	61.4	1,865	61.0	1	Reference	1	Reference
1–11	481	12.7	369	12.1	0.88	0.76, 1.02	0.90	0.77, 1.05
12–23	244	6.4	188	6.2	0.90	0.74, 1.10	0.86	0.70, 1.06
≥24	726	19.1	630	20.6	1.01	0.90, 1.14	1.05	0.92, 1.19

* Because of missing data, some categories do not sum to 100%. $N = 3,499$ cases and 4,213 controls.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age and state of residence.

§ Adjusted for age, state of residence, weight at age 18 years, screening mammograms per year over the last 5 years, and all variables in tables 1 and 2.

¶ Parous women only.

TABLE 2. Odds ratios and 95% confidence intervals for factors modifiable after menopause in relation to postmenopausal invasive breast cancer risk, Wisconsin, Massachusetts, and New Hampshire, 1997–2001

Factor	No. of controls	%*	No. of cases	%*	OR†,‡	95% CI†	OR§	95% CI
Postmenopausal hormone use (type and duration)								
Never	2,125	50.4	1,583	45.2	0.95	0.80, 1.12	0.92	0.77, 1.10
Former	364	8.6	283	8.1	1	Reference	1	Reference
Current estrogen only	839	19.9	651	18.6	0.98	0.81, 1.18	0.96	0.79, 1.17
Current estrogen + progestin	638	15.1	741	21.2	1.48	1.23, 1.79	1.31	1.07, 1.60
Current other/unknown	198	4.7	191	5.5	1.25	0.97, 1.61	1.08	0.83, 1.41
Recent alcohol consumption (drinks/week)¶								
<1.0	2,364	56.1	1,819	52.0	1	Reference	1	Reference
1.0–6.9	1,253	29.7	1,099	31.4	1.14	1.03, 1.26	1.12	1.00, 1.24
7.0–13.9	400	9.5	358	10.2	1.19	1.02, 1.39	1.14	0.96, 1.34
≥14.0	164	3.9	189	5.4	1.51	1.22, 1.88	1.43	1.14, 1.80
Weight change since age 18 years (kg)								
Lost >5	123	2.9	85	2.4	1.02	0.75, 1.37	1.09	0.79, 1.49
Lost ≤5–gained ≤5	770	18.3	521	14.9	1	Reference	1	Reference
Gained 5.1–15	1,282	30.4	1,079	30.8	1.24	1.08, 1.43	1.27	1.10, 1.47
Gained 15.1–30	1,445	34.3	1,269	36.3	1.28	1.12, 1.47	1.36	1.18, 1.56
Gained >30	455	10.8	456	13.0	1.47	1.24, 1.75	1.67	1.39, 2.00
Recent recreational physical activity (hours/week)#								
0	1,565	37.2	1,325	37.9	1.17	0.92, 1.50	1.26	0.98, 1.61
0.1–2.0	1,732	41.1	1,417	40.5	1.13	0.88, 1.43	1.15	0.90, 1.48
2.1–5.0	722	17.1	616	17.6	1.17	0.90, 1.51	1.17	0.90, 1.53
>5.0	172	4.1	125	3.6	1	Reference	1	Reference

* Because of missing data, some categories do not sum to 100%. $N = 3,499$ cases and 4,213 controls.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age and state of residence.
§ Adjusted for age, state of residence, weight at age 18 years, screening mammograms per year over the last 5 years, and all variables in tables 1 and 2.
¶ Over the past year.
# Averaged over the period 6 years to 1 year prior to the participant's reference date.

The sensitivity of the PAR estimates to cutpoint selections was examined. If the reference category for weight gain was expanded to include gains of as much as 15 kg, the PAR decreased to 8.8 percent (95 percent confidence interval: 4.4, 12.7). If the reference category for physical activity was expanded to include as little as 2 hours per week of exercise, the PAR decreased to 3.9 percent (95 percent confidence interval: −4.7, 12.7). With both of these modifications, the summary PAR for the four factors considered modifiable after menopause was 22.0 percent (95 percent confidence interval: 10.4, 31.7).

DISCUSSION

The results of this study suggest that modifying risk factors later in life could substantially reduce postmenopausal breast cancer incidence in the United States. Approximately 40 percent of postmenopausal cases of invasive breast cancer could be eliminated if all women ceased or did not initiate postmenopausal hormone use, restricted alcohol consumption to less than one drink per week, avoided weight gain of more than 5 kg after age 18 years, and exercised more than 5 hours per week.

PAR estimates are highly dependent on the cutpoints chosen to represent exposed status for each factor (7). Thus, cutpoints should be carefully noted in interpreting and comparing PAR estimates. In this study, extreme cutpoints were used, such that the PARs likely represent an upper limit regarding the proportion of cases of breast cancer that could be eliminated by changing the risk factor distribution in the population. Whether weight gain and low physical activity could be altered by such a radical degree in the United States, as suggested by our cutpoints, is debatable. However, it is instructive to know the potential effect of public health efforts directed toward these ends.

TABLE 3. Population attributable risks for postmenopausal invasive breast cancer, Wisconsin, Massachusetts, and New Hampshire, 1997–2001

Risk factor	Summary PAR*		Individual PAR	
	PAR%†	95% CI*	PAR%†	95% CI
Factors not modifiable after menopause	57.3	47.5, 65.4		
Reproductive and menstrual factors	42.2	30.7, 51.8		
Age at menarche			18.8	7.9, 29.0
Age at menopause			13.7	6.6, 19.6
Age at first full-term pregnancy‡			5.2	−3.2, 13.9
Parity			13.3	6.9, 19.8
First-degree family history of breast cancer			8.5	6.5, 10.5
Personal history of benign breast disease			9.7	7.3, 12.0
Height at age 25 years			11.0	3.5, 18.5
Factors modifiable after menopause	40.7	23.0, 55.1		
Current postmenopausal hormone use§			4.6	−3.5, 11.9
Recent alcohol consumption (past year)			6.1	2.1, 10.3
Weight gain since age 18 years¶			21.3	13.1, 29.3
Recent recreational physical activity#			15.7	−6.5, 33.7

* PAR, population attributable risk; CI, confidence interval.

† Assumes all participants move to the lowest risk category of factor or combination of factors, while other variables are held constant. For participants missing data for a variable, assumes no change in risk according to that variable. Adjusted for age, state of residence, weight at age 18 years, screening mammograms per year over the last 5 years, and all variables in tables 1 and 2.

‡ Among parous women only.

§ Assumes no change in risk for never users.

¶ Assumes no change in risk for women who lost more than 5 kg.

Averaged over the period 6 years to 1 year prior to the participant's reference date.

Multiple studies to date have reported summary PARs for sets of risk factors not amenable to modification (4, 5, 7). Other studies have included modifiable risk factors combined with nonmodifiable factors, without conducting separate analyses for modifiable versus nonmodifiable factors (3, 6). In the only previous study known to report a summary PAR associated with a set of modifiable factors, Mezzetti et al. (8) found a PAR of 33 percent for low β-carotene intake, alcohol consumption of more than 20 g per day, and low physical activity. A summary PAR of 40 percent was also reported for low physical activity and overweight body mass index.

A number of studies have reported the PAR associated with individual modifiable risk factors, including diet (8, 14), body weight (8, 15, 16), physical activity (8, 17), alcohol consumption (8, 17–20), and postmenopausal hormone use (6, 17, 21–23). In the only previous study known to evaluate a PAR for weight gain, Eliassen et al. (16) found a PAR of 15 percent for a gain of 2 kg or more since age 18 years. Clarke et al. (17) and Mezzetti et al. (8) estimated PARs of 15 percent and 12 percent, respectively, for physical inactivity. In our population, we found PARs of 21.3 percent for weight gain of more than 5 kg and 15.7 percent for 5 or fewer hours of weekly physical activity. Our estimate of a PAR of 6.1 percent for alcohol consumption is within the wide range of estimates (2–25 percent) previously obtained (8, 17–20).

We found a PAR of 4.6 percent for current postmenopausal hormone use. We are unaware of previous estimates for this effect of changing current hormone users to former users. Our estimate of 8.5 percent for converting all women to never users is similar to the PAR of 11 percent observed by Clarke et al. (17) in a population of California women. Notably, both studies collected data prior to publication in 2002 of results from the Women's Health Initiative indicating that the risks of postmenopausal hormone therapy outweigh the benefits (24). Since this time, use of postmenopausal hormones has declined rapidly in the United States (25–27). Conversely, the prevalence of obesity continues to increase (28), suggesting that the PAR for obesity may also increase.

Between-study variation in the PAR for a risk factor can often be attributed to dependence of the PAR on the prevalence of exposure to that factor in the population. Therefore, results in one population should be extrapolated to another population with caution, and with particular attention to the prevalence of risk factors of interest in each population. This study was limited to postmenopausal women; notably, the direction and magnitude of effect for certain breast cancer risk factors depend on menopausal status (1, 29, 30). Participants were 95.6 percent non-Hispanic White and therefore our results may not be representative of those for the United States as a whole or for specific areas with more diverse populations.

Study design may also influence PAR estimates and account for between-study variation. As with any case-control study, the potential for selection bias, recall bias, and measurement error must be acknowledged. Any bias in obtaining our odds ratio estimates could influence the PAR estimates in either direction. Nondifferential exposure misclassification would bias odds ratio estimates toward the null, and Hsieh and Walter (31) have shown that this effect would result in an underestimate of the true PAR.

The formula used here for the PAR assumes that there is a causal relation between the risk factors and the disease, that exposure to the risk factor(s) can be eliminated while other variables remain constant, and that the disease is rare such that odds ratios can be used as relative risk estimates. Notably, we focused on risk factors that have been consistently associated with breast cancer risk. However, causality for most of these risk factors has not been definitively established, and thus caution must be taken in interpreting these results.

Because the PAR is often misinterpreted (12), its limitations must be clearly acknowledged. PARs associated with single risk factors cannot be summed to derive the total PAR attributable to all the factors, nor should the individual PARs for all risk factors sum to 100 percent (2, 12, 32). Thus, the PAR for established risk factors cannot be subtracted from 100 percent to indicate the proportion of disease risk explained by a yet-to-be-identified set of factors.

The relevance of PARs to public health is minimal when the factors under consideration are not modifiable (12). We focused on factors that are modifiable later in life, using variables representing current or recent lifestyle behaviors. Many of these factors, including weight change, physical activity, and alcohol consumption, are also modifiable earlier in life. Notably, recent behaviors may be correlated with earlier life behaviors that also influence breast cancer risk. For instance, the increased risk associated with recent physical inactivity may be partially due to inactivity earlier in life, and this increased risk may not be totally eliminated by initiating better exercise habits. We were able to investigate this issue by using data on lifetime physical activity habits. In models adjusted for recreational physical activity between age 22 years and menopause, the PAR for recent (5-year) recreational physical activity was reduced somewhat to 11.6 percent (95 percent confidence interval: −6.3, 26.6). The increased risk associated with other factors, such as hormone use and alcohol consumption, is thought to dissipate relatively quickly after cessation, although duration of use likely is important (33, 34). In this regard, the PAR attributed to these factors appears to be a reasonable estimate of the potential, immediate impact of lifestyle changes later in life.

Invasive breast cancer is a heterogeneous disease (35). We did not have data regarding hormone status or other phenotypic markers and thus were unable to consider such heterogeneity. A number of risk factors, including parity, age at first birth, and obesity, are more strongly associated with estrogen receptor–positive than estrogen receptor–negative tumors (36). Thus, it is possible that we underestimated the PAR of these factors for estrogen receptor–positive tumors and overestimated the PAR for estrogen receptor–negative tumors.

Finally, caution must be taken when risk factors for one disease may be protective factors for other diseases. For example, although alcohol consumption is a risk factor for breast cancer, consumption of moderate amounts is associated with a reduced risk of cardiovascular disease (37, 38). Thus, public health efforts must weigh these competing outcomes.

In summary, a substantial proportion of postmenopausal cases of breast cancer could be prevented by modifying known risk factors. While these findings provide a target for public health strategies, dramatic alterations in the lifestyle of the majority of the population would be required. These results provide further evidence that cancer incidence can most effectively be reduced by population-based strategies to shift the entire distribution of risk factors, rather than focusing on high-risk subgroups (39).

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