RESEARCH COMMUNICATION

Association of Lifestyle and Other Risk Factors with Breast Cancer According to Menopausal Status: A Case-Control Study in the Region of Western Pomerania (Poland)

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Abstract

Purposes: The purpose of this study was to examine the association between family history, reproductive, anthropometric, lifestyle factors and risk of breast cancer according to menopausal status, using data from a case-control study conducted in the Region of Western Pomerania (Poland). Methods: A total, 858 women with histological confirmed breast cancer and 1085 controls, free of any cancer diagnosis, aged 28-78 years, were included in the study. The study was based on a self-administered questionnaire. Logistic regression was used to compute odds ratios and 95% confidence intervals and a broad range of potential confounders was included in analysis. Results: Protective effect of a late age at menarche, a longer period of breast-feeding, increased levels of: recreational physical activity, total vegetables or fruits intake, and intake of vitamins on the risk of breast cancer was observed among both pre- and post-menopausal women. Familial history of breast cancer, active or passive smoking, experience of a crude psychological stress were positively associated with breast cancer regardless menopausal status. Current body weight, current body mass index, increased alcohol intake elevated breast cancer risk in postmenopausal women, while these factors did not alter risk among premenopausal women. Increased consumption of red meat or animal fats elevated the risk in premenopausal women. More educated premenopausal women had lower breast cancer than those graduated from elementary school. Low family income increased the risk in premenopausal women. Conclusion: There is evidence for a dose-response relationship between several lifestyle factors and breast cancer risk. The results also suggest that some different mechanisms may operate in breast cancer etiology in pre-and post-menopausal women. A multifactorial process of breast cancer development, the complex interaction between physical activity, diet, energy intake and body weight, inconsistent and inconclusive data on breast cancer risk factors coming even from well-designed epidemiological studies are the case for continual update knowledge on primary prevention and identification of changes in behavior that will reduce the risk.

Key words: Breast cancer - case-control study - lifestyle - menopausal status - risk factors

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Introduction

Breast cancer (BC) is the second to lung leading cause of death due to neoplasia among women in USA and western countries (Jemal et al., 2003). It has been established that one of the strongest predictors of women risk of BC are: increasing age, geographic region, family history of this disease and genetic factors such as mutations in BRCA1 and BRCA2 genes (Antoniou et al., 2005) and in other high-penetrance genes (e.g., p53) (Dumitrescu & Cotarla, 2005). The next well established factors that increase BC risk included exposure on ionizing radiation in childhood, lifetime exposure to endogenous sex hormones determined by reproductive factors (Kelsey et al., 1993; Minami et al., 1997; Veronesi et al., 2005) (early age at menarche, <12 years; late age at menopause, >54 years; nulliparity; late age at first full term pregnancy, >30 years; high mammografic breast density (Boyd et al., 1995), and high insulin-like growth factor 1 (IGF1) concentration (Norat et al., 2007).

Over the past two decades numerous investigations have focused on the possible role of lifestyle factors. Strong evidence exists that oral contraceptives (OCP) recent use, hormonal replacement therapy (HRT), smoking, physical inactivity, increased alcohol consumption (about 1 drink/day, ≈10g alcohol), obesity (in postmenopausal women), diet rich in high saturated fatty acids and red meat are associated with increased BC risk (Colditz et al., 2000; McPherson et al., 2000; Hulka and Moorman, 2001; Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Stasiolek et al., 2002; Nkondjock et al., 2003; Key et al., 2004; Nkondjock et

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al., 2006). Resent studies have also found a positive association between experience of psychological stress and BC risk (Lillberg et al., 2003; Kruk and Aboul-Enein, 2004).

Strong evidence exists that increased physical activity reduces the risk of BC even by 70% in most physically active women see, e.g.(Friedenreich and Orenstein, 2002; AICR, 2005; Kumar et al., 2005; Kruk, 2006; Kruk, 2007; Miles, 2007; Monninkhof et al., 2007). Also, intake of vegetables and fruits, higher parity and longer term of breast feeding have been recognized as factors that decrease the risk (Nkondjock et al., 2003; Key et al., 2004; Dumitrescu and Cotarla, 2005).

Recognized BC risks contribute to a better understanding etiology of the disease but they only explain a small proportion of cancer patients. It is known that physical activity, diet, energy intake and body weight exert effect on BC risk independently as well as these determinants of lifestyle undergo the complex interaction (AICR, 2005). Similarly, reproductive factors are also interrelated. Furthermore, mechanisms responsible for developing BC may be different among subgroups of women, e.g. in pre- and post-menopausal women. Some of behavioral risk factors may be easily modified (McTiernan, 2003), thereby their modification may play an important role in the prevention of BC.

Recommendations for BC prevention need still more precise data that consider several variables which have been identified as well confirmed risk factors, and those probable, taking in account a woman's menopausal status. This study was designed to evaluate BC risk factors among Polish women with a particular focus on differences and similarities in the risk factors between pre- and post-menopausal women.

Materials and Methods

Subjects

This study was conducted between January 2003 and May 2007 in the Region of Western Pomerania. The study received Ethics Committee Approval from the Pomeranian Medical Academy (no. BN-001/254/02, 09 December 2002) in accordance with assurances approved by the Polish Department of Health and Human Services. Case subjects were women identified from the Szczecin Regional Cancer Registry that covered the mentioned geographic region. These cases were diagnosed with histologically confirmed invasive BC, and operated during 1999 to 2006. Cases were included in the study if they were aged 28-78 years, were not terminally ill and had not secondary BC. During this study period, 2409 cases were identified as potentially eligible and were sent an invitation and written informed consent. Of these women, 1222 could not be contacted. Reasons for ineligibility included a lack of reply, death, a woman's own refusal, and changed address. The remaining eligible women, 1187 (49.3%) agreed to participate in the study and provided written informed consent. Then, self-administered questionnaires in stamped, preaddressed envelopes were sent to complete and return to 1187 case subjects. Of these women, 881 (74.2%) completed the questionnaire, 262 (22.1%) refused to participate, 13 (1.1%) could not be contacted, and 31 (2.6%) had to many missing data. Finally, 858 cases were included in the statistical analyses. Overall response rates (participants interviewed/participants suitable and available for an review for cases was 74.2% (881/1187).

Controls were frequency matched on 5-year age group, and place of residence (urban, rural). They were required to have no personal history cancer and earlier physical limitation. Of the 1615 controls contacted, 1189 women (73.6%) agreed to participate in a study and gave their consent to receive the study package to complete and return. Of these controls, completed questionnaires were received from 1121 (94.3%). The reasons for refusal were mainly a lack of interest or privacy. Information collected from 36 controls was considered incomplete (to many missing data), and they were excluding from analysis. Finally, 1085 controls were included in analysis as the referents; an overall response rate for controls was 69.4% (1121/1615). Most of the controls included in the analysis (853 women, 78.6%) was selected among patients admitted to ambulatories in the same area as cases for health controlling. Remaining 232 control subjects were selected from hospital patients treated for fractures or sprains (5.4%), cardiovascular diseases (3.1%), disc disorders and back pain (2.8%), and other diseases, such as skin, eye, laryngological (10.1%). The ratio of cases to controls included in the analysis was 1:1.26.

Data Collection

All participants filled in a 8-page self-administered questionnaire including questions about health status, socio-demographic characteristics, reproductive factors, family history of BC, current weight and height, lifestyle habits (physical activity, dietary habits, sleeping, tobacco smoking, alcohol consumption, experience of psychological stress, use of hormones, multivitamins supplement, medical and screening history). Weight and height were used to calculate body mass index (BMI) using Quetelet' formula of weight in kg divided by height^2 (m^2). All data were obtained up to the reference year (the year before diagnosis for cases or the year before selection into the study for controls). Information on dietary intake and alcohol consumption during the reference year (a separate section of a questionnaire), was gathered from each subject modelling on the Block et al. (1990), and Franceschi et al. (1993) food frequency questionnaires. The section included 18 main Polish-specific food groups e.g., red meats (boiled, fried, canned) and alternatives, milk and its products, grain products, vegetables and fruits, sweets, desserts, unsaturated and saturated fats. Participants were asked to report types of foods and beverages including juices, milk and alcoholic drinks as well as the frequency of their consumption per week and portion size for food. Tobacco use was estimated in terms of usual number of cigarettes smoked per day regularly during the reference year or in past by a woman or a woman's life partner.

Several studies identify stressful life events or bereavement with increased risk of breast cancer (Ginsberg et al., 1996). To obtain data on the women' life experiences starting from such event as a change in residence to major

events such as the death of a spouse, a child, the questionnaire contained a question: "Did you experience a strong psychological stress? If so, please specify its kind". Women were asked to indicate which life events they had encountered, among 11 items comprising the widely known 43-item Holmes and Rahe (1967) social readjustment rating scale. In addition, the respondents were asked how many years/months had passed since the event had taken place.

To assess physical activity the respondents were asked to complete separate sections of the questionnaire including a comprehensive assessment lifetime household and occupational activities, and leisure-time activities. Details about physical activity were recorded in a table format using modified versions of the Friedenreich et al (1998) and Kriska et al (1990). questionnaires. Briefly, participants were asked to indicate kinds of recreational activities among defined by 43 popular activities including organized sports activities (team activities, school sports) and individual activities including walking, cycling, running, swimming, exercise in fitness club, dancing, jogging, gardening, and other. The intensity of activity was ascertained by recording the subject's self-reported intensity levels and in terms of metabolic equivalent (MET) abstracted from the Compendium of Physical Activities (Ainsworth et al., 2000), representing the number of kilocalories per hour expended by each kilogram of body weight (Pate et al., 1995). Total lifetime physical activity was calculated as the sum of household, occupational and recreational activity. The sport/ recreational activity was categorized as light (<3 METs), moderate (3÷6 METs), vigorous (>6 METs) – intensity, based on current physical activity recommended levels of the activity for breast cancer prevention (Pate et al., 1995; Kumar et al., 2005) (less than 30 min 5 days per week, 30-60 min 5 days per week and 60 min 5 days per week, respectively).

Statistical analysis

Relationships between lifestyle and other risk factors were estimated by analysis of variance. Logistic regression analysis was used to obtain odds ratios (ORs) and the 95% confidence interval (95%, CI) as estimates of relative risks. The main outcomes were incident cases of cancer, i.e., women with invasive BC after mastectomy. The main independent variable was variable for given category (e.g.,

Table 1. Selected Characteristics of the Study Subjects

Variables	Cases N=858		Controls N=1085		p-value
Age (years) in reference year, mean (SD*)	55.3	(9.7)	54.8	(9.5)	0.24
Education level					
Elementary school	262	(30.5)	253	(23.3)	
Middle school	339	(39.5)	379	(34.9)	
High school (university, academy)	257	(30.0)	453	(41.8)	<0.0001
Marital status (number, %)					
Never married	51	(5.9)	56	(5.2)	
Married	580	(67.6)	736	(67.8)	
Widowed/divorced	227	(26.5)	293	(27.0)	0.74
Systematic control of breast (yes)	606	(90.2)	606	(85.2)	0.0052
Height (cm), mean (SD*)	161.8	(5.7)	162.6	(5.6)	0.005
Current body weight (kg), mean (SD)	68.6	(12.4)	66.9	(11.2)	0.0012
Body mass index (kg/m^2), mean (SD)	26.2	(4.7)	25.3	(4.1)	0.0001
Age at menarche (years), mean (SD)	13.82	(1.61)	13.80	(1.57)	0.76
Parity	1.90	(1.10)	1.91	(1.03)	0.80
Age at first birth (years), mean (SD)	23.35	(3.94)	23.97	(3.95)	0.09
Age at menopause (years), mean (SD)#	48.7	(5.3)	49.22	(4.65)	0.07
Breast-feeding (months), mean (SD)	6.62	(7.52)	10.82	(10.37)	<0.0001
Red meat consumption (servings/week), mean (SD)	2.24	(1.66)	2.10	(1.45)	0.086
Saturated fat consumption (servings/week), mean (SD)	5.12	(2.70)	4.15	(2.72)	0.0001
Alcohol drinking (drinks‡/week), mean (SD)	1.2	(0.87)	1.14	(0.95)	0.27
Vegetable consumption (servings/week), mean (SD)	3.35	(2.25)	4.31	(2.38)	<0.0001
Fruits consumption (servings/week), mean (SD)	5.24	(2.63)	5.62	(2.41)	0.0009
Ever users of OCP (number, %)	153	(17.8)	158	(14.6)	<0.011
Ever users of HRT (number, %)	301	(35.1)	371	(34.2)	0.68
Stress experience (yes, number, %)	492	(57.3)	497	(45.8)	<0.0001
Active smokers (number, %)	413	(48.2)	355	(32.8)	<0.0001
Passive smokers (number, %)	458	(55.7)	347	(32.6)	<0.0001
Family history of breast cancer in first degree female relatives (number, %)	138	(16.1)	82	(7.6)	<0.0001
Total lifetime physical activity, mean (SD) MET-hours/week/year	137.6	(66.7)	158.5	(73.34)	<0.0001
Total lifetime sports/recreational physical activity (MET-h/week/year)	21.15	(33.07)	27.91	(24.04)	<0.0001

*SD, standard deviation; MET, metabolic equivalent; HRT, hormonal replacement therapy; OCP, oral contraceptives; ‡ one alcoholic drink, tin of beer or a small bottle, 125ml of wine or 30g of high-grade alcohols; † due to missing values, some categories do not sum to 100%; # among postmenopausal women only.

lifestyle variable, reproductive variable), which was entered as dummy variable. Two sets of analyses were performed. In the first model ORs were adjusted only for age. In the second model, multivariate analysis was applied to control for confounding factors. Models included adjustment for age (continuous) and other known in research literature risk factors and potential confounders that were selected a priori: place of residence (urban/rural), education, family income average over the past 10 years, marital status, BMI, age at menarche, menstrual cycles, age at first birth, number of pregnancies, duration of breast feeding, use of OCP, use of HRT, family history of BC in first-degree relatives, age at menopause, control of breast, smoking status, alcohol intake, dietary habits, screening mammography or ultrasonic examination (USG), and physical activity, classified as in Table 2.

For all potentially confounders, missing data were classified as unknown. Discriminant analysis was performed in order finding an optimal model; the effect of adding and removing confounders on a model was evaluated by F-Fisher's test. Models were run separately for both pre- and post-menopausal women. Women were considered to be postmenopausal if they reported being postmenopausal and had no menstrual periods at least one year before their reference data and no hormonal therapy or they had reached the age of above 55 years and reported a lack of menstruation. The remaining women and also those women who reported hysterectomy or taking HRT and if their reference date was under 42 years were considered as premenopausal. The final models included only those confounding variables that were found to influence the goodness of the model fit, and were associated statistically significantly with BC and a risk factor, as noted in the footnotes to the tables given in the paper.

Dose-response trends in the risk calculation were evaluated for all analyses by fitting the continues variable into the model using the Wald __ value (Greenland, 1998), logistic analog to the Mantel-Haenszel trend (Schlesselman, 1982). Effect of modification was examined by inclusion of cross-product interaction terms in loglinear models. Descriptive characteristics were performed to characterize the study group and to examine case-control differences. The differences were assessed using chi-square (χ^2)test for categorical variables and t-test for differences in means. All P values are two sided and a P-value less than 0.05 is considered as statistically significant. All analyses were done on a PC using statistical package STATISTICA 98 (stat Soft Polsca, Kraków, Poland).

Results

Table 1. summarizes the characteristics of participants by case and controls status. The mean age of the subjects was 55.3±9.7 years for cases and 54.8±9.5 years for controls (p=0.24). Cases and controls were similar in term of average age, age at menarche, age at menopause, frequency of red meat and alcohol intake, parity, marital status, and HRT use. Compared with controls, cases were somewhat lower and less educated, were younger at first birth, had higher body weight and BMI, reported shorter duration of breast-feeding, were more likely to have had a family history of BC in mother or a sister/sisters and to be ever active and passive cigarette smokers and users of oral contraceptives. Cases also had lower lifetime averages for total and sports/recreational physical activity, and were more likely to consume vegetables and fruits rarely. In addition, there was noticeable difference between cases and controls for a stress experience with excess of case subjects. As expected, cases were more likely than controls to examine breast.

Menopausal status appeared to modify the relation between BC risk and several lifestyle variables. The multivariable adjusted ORs with 95% CIs for BC in separate strata by menopausal status and values of P for interaction are presented in Table 2. The ORs were similar to those in univariate analyses i.e., adjusted for age (data not shown). Strong protective effect of later age at menarche, increased duration of breast-feeding, high intake of vegetables, fruits and use of vitamins supplementation, leisure-time physical activity at least 7.5 MET-h/week/year was observed in both pre- and post-menopausal women (P<0.01 for trend). The reduction in the risk associated with parity was stronger for postmenopausal women (OR=0.60; 95% CI, 0.38-0.94; 2 pregnancies versus nulliparous women), but the test for interaction was not significant (χ^2=2.5; df=3; P for interaction 0.48). There was a positive association between active and passive cigarette smoking, experience of psychological stress and BC risk among both subgroups of women (Ptrend≤0.0001 for smoking, Pvalue≤0.002 for stress). The risk increase among women with a family history of BC appeared to be larger in postmenopausal women than in those premenopausal (OR=3.18, 95% CI, 2.16-4.69; OR=1.43, 95% CI, 1.03-2.28, χ^2=6.7, df=1, P for interaction significant=0.01), respectively.

Current body weight and BMI were positively associated with BC risk among postmenopausal women, (ORs: 1.80, 2.62, respectively); higher levels of each predicted higher BC risk (Pfor trend = <0.0001, <0.0001, respectively). For alcohol intake, an increase in risk was also stronger among postmenopausal women (OR=2.07; 95% CI, 0.57-4.66; ≥2 drinks/week, versus never) than premenopausal women (OR=0.66; 95% CI, 0.90-3.05), but the test for interaction was nonsignificant (χ^2=2.8, df=2, P for interaction =0.25). Hormonal replacement therapy use was not associated with increased BC risk in postmenopausal women. The statistically significant BC risk increments for increased red meat (≥5 servings/week versus 0) and fat consumption (≥3 times/week versus 0) was observed in premenopausal women, but the tests for interaction were not significant (χ^2=4.3, df=4, P for interaction=0.37 and χ^2=0.04, df=1, P for interaction 0.85, respectively). Also, the premenopausal women having low family income had increased the risk compared with those having high income (P for interaction significant). More educated subgroup of women had lower BC than that graduated from elementary school. Height, age at first childbirth, sleeping time showed no associations with BC risk in either pre- or post-menopausal women.

Table 2. Multivariable Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer in Relation to Anthropometric, Reproductive, Lifestyle and other Variables, by Menopausal Status

Variable	Premenopausal		Postmenopausal	
	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95%) CI)
Current body weight (kg)				
<62	121/197	1.00[a]	139/226	1.00[a]
62-70	108/144	1.29 (0.92-1.80)	178/171	1.70 (1.26-2.30)
>70	81/134	1.03 (0.71-1.47)	231/213	1.80 (1.35-2.39)
P for trend		0.76		<0.0001
		P for interaction = 0.04		
Height (cm)				
≤157	43/61	1.00[b]	117/110	1.00[b]
158-162	97/145	0.95 (0.56-1.62)	189/184	1.11 (0.77-1.62)
163-166	96/141	0.96 (0.57-1.62)	142/188	0.88 (0.60-1.30)
>166	74/128	0.90 (0.52-1.56)	100/128	0.82 (0.54-1.23)
P for trend		0.66		0.17
		P for interaction = 0.55		
Current BMI (kg/m2)				
<22.5	103/148	1.00[a]	78/157	1.00[a]
22.6-<25.0	84/129	0.94 (0.61-1.45)	127/138	1.85 (0.98-2.84)
25-<30	90/154	0.75 (0.49-1.16)	221/218	2.13 (1.45-3.13)
≥30	33/44	1.34 (0.72-2.49)	122/97	2.62 (1.66-4.11)
P for trend		0.60		<0.0001
		P for interaction = 0.002		
Age at menarche				
≤12	60/28	1.00[b]	98/231.00[b]	
13	86/214	0.16 (0.09-0.28)	117/195	0.13 (0.07-0.22)
≥14	166/233	0.33 (0.20-0.55)	333/392	0.20 (0.12-0.33)
P for trend		<0.0093		<0.0001
		P for interaction = 0.23		
Age at first childbirth				
<22	94/98	1.00[d]	180/180	1.00[d]
22-29	165/295	0.63 (0.44-0.91)	287/343	0.96 (0.73-1.27)
≥30	19/33	0.70 (0.35-1.41)	26/47	0.57 (0.32-1.09)
P for trend		0.064		0.16
		P for interaction = 0.18		
Number of pregnancies				
0	31/48	1.00[a]	55/39	1.00[a]
1	67/101	1.03 (0.58-1.78)	121/146	0.57 (0.35-0.92)
2	156/239	1.06 (0.64-1.74)	238/273	0.60 (0.38-0.94)
≥3	56/87	1.01 (0.57-1.79)	134/152	0.63 (0.27-1.49)
P for trend		0.96		0.25
		P for interaction = 0.48		
Months of breast feeding				
0	31/48	-	55/39	-
<6	190/202	1.00[d]	336/255	1.00[d]
6-12	48/86	0.58 (0.38-1.87)	97/120	0.62 (0.45-0.85)
>12	40/139	0.30 (0.20-0.45)	59/195	0.23 (0.17-0.32)
P for trend		<0.0001		<0.0001
		P for interaction = 0.31		
Family history of breast cancer				
No	273/433	1.00[e]	448/570	1.00[e]
Yes	38/42	1.43 (1.03-2.28)	100/40	3.18 (2.16-4.69)
		P for interaction = 0.01		
Smoking status				
Non-smokers	134/305	1.00[b]	310/424	1.00[b]
Active smokers				
<10 sticks/day	69/74	2.09 (1.42-3.09)	92/72	1.73 (1.23-2.44)
≥10 sticks /day	106/96	2.55 (1.81-3.60)	146/113	1.78 (1.33-2.37)
P for trend		<0.0001		<0.0001
		P for interaction = 0.29		

Table 2. Continued. Multivariable Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer in Relation to Anthropometric, Reproductive, Lifestyle and other Variables, by Menopausal Status

Variable	Premenopausal		Postmenopausal	
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)
Passive smoking				
Non-smoker husband	199/298	1.00[c]	244/420	1.00[f]
Smoking husband				
<20 sticks/day	77/90	2.16 (1.49-3.14)	133/108	2.11 (1.56-2.85)
≥20 sticks/day	109/73	3.79 (2.63-5.47)	139/76	3.15 (2.28-4.35)
P for trend		<0.0001		<0.0001
		P for interaction = 0.77		
Alcohol consumption				
Never	108/163	1.00[a]	257/328	1.00[a]
≤1 drink/week	131/240	0.82 (0.59-1.14)	203/227	1.13 (0.87-1.45)
≥2 drinks/week	69/71	1.66 (0.90-3.05)	85/54	2.07 (1.57-4.66)
P for trend		0.28		0.0021
		P for interaction = 0.25		
Red meat consumption				
0	31/76	1.00[b]	95/109	1.00[c]
1 serving/week	71/110	1.60 (0.95-2.67)	115/117	1.10 (0.75-1.61)
2 servings/week	113/166	1.66 (1.02-2.70)	194/233	0.92 (0.66-1.29)
3-4 servings/week	65/65	1.66 (0.98-2.83)	99/117	0.94 (0.64-1.39)
≥5 servings/week	29/24	2.96 (1.49-5.91)	44/33	1.51 (0.89-2.57)
P for trend		0.0091		0.65
		P for interaction = 0.37		
Animal fat consumption				
<1-2 times/week	42/92	1.00[b]	106/158	1.00[c]
≥3 times/week	267/383	1.65 (1.15-2.41)	441/451	1.35 (0.93-1.95)
		P for interaction = 0.85		
Vegetables consumption				
≤4 servings/week	158/187	1.00[g]	270/224	1.00[f]
5-6 servings/week	79/145	0.64 (0.45-0.91)	132/179	0.60 (0.45-0.81)
≥7 servings/week	71/142	0.59 (0.41-0.84)	143/203	0.58 (0.44-0.77)
P for trend		0.0018		<0.0001
		P for interaction = 0.97		
Fruits consumption (included juices)				
≤5 servings/week	109/116	1.00[a]	194/151	1.00[a]
5-6 servings/week	56/112	0.53 (0.35-0.81)	115/167	0.54 (0.39-0.74)
≥7 servings/week	149/246	0.61 (0.43-0.85)	230/289	0.62 (0.47-0.81)
P for trend		0.0062		0.0012
		P for interaction = 0.99		
Intake of vitamins				
No	69/76	1.00[a]	134/90	1.00[a]
Yes	241/399	0.68 (0.47-0.98)	414/519	0.53 (0.40-0.72)
		P for interaction = 0.36		
Stress experience				
No	148/277	1.00[b]	218/311	1.00[b]
Yes	162/198	1.62 (1.20-2.20)	330/299	1.68 (1.31-2.16)
		P for interaction = 0.88		
Sleeping time				
<7 h/day and night	89/163	1.00[b]	165/191	1.00[b]
≥7 h/day and night	221/313	1.35 (0.97-1.86)	383/418	1.10 (0.85-1.44)
		P for interaction = 0.32		
OCP use				
No	229/385	1.00[b]	476/542	1.00[b]
Yes	81/90	1.65 (1.15-2.36)	72/68	1.35 (0.93-1.95)
		P for interaction = 0.36		
HRT				
No			341/372	1.00[e]
Yes			207/238	0.93 (0.74-1.19)
Sports/recreational physical activity[‡], MET-h/week/year				
0-7.49	139/86	1.00[g]	302/147	1.00[g]
7.50-14.99	33/56	0.36 (0.22-0.60)	65/90	0.35 (0.25-0.53)
>15	138/333	0.26 (0.18-0.36)	181/373	0.24 (0.18-0.31)
P for trend		<0.0001		<0.0001
		P for interaction = 0.93		

Table 2. Continued

Education level				
≤12	60/28	1.00[b]	98/23	1.00[b]
Elementary school	84/65	1.00[h]	178/188	1.00[c]
Middle school	117/163	0.62 (0.41-0.95)	222/216	1.06 (0.80-1.40)
High school (university, academy)	109/247	0.42 (0.23-0.64)	148/206	0.76 (0.56-1.02)
P for trend		<0.0001		0.063
		P for interaction = 0.004		
Family income				
High	223/369	1.00[c]	390/428	1.00[c]
Middle	62/84	1.22 (0.84-1.76)	130/146	0.98 (0.74-1.29)
Low	24/18	2.22 (1.17-4.19)	24/32	0.82 (0.62-1.09)
P for trend		0.015		0.59
		P for interaction = 0.05		

OR, odds ratio; CL, confidence intervals; OCP-oral contraceptive; HRT-hormonal replacement therapy; MET-metabolic equivalent; BMI, body mass index; [a]Adjusted for age, recreational activity, breast-feeding, stress, passive smoking. [b]Adjusted for age, recreational activity. [c]Adjusted for age. [d]Adjusted for age, BMI, stress experience active and passive cigarette smoking. [e]Adjusted for age, BMI, stress experience, passive cigarette smoking. [f]Adjusted for age, breast-feeding. [g]Adjusted for age, age at menarche. [h]Adjusted for age, recreational physical activity, breast-feeding. ‡Categories of physical activity: 0-7.49, 7.50-14.99, >15 are equivalents to about <2.5 h/week, 2.5-5.0 h/week and >5 h/week at a level of 3 MET.

Discussion

This large case-control study provides the simultaneous description and analysis of modifiable BC risk factors as well as those that are not easily amenable for intervention. Statistical analyses were performed separately for pre- and post-menopausal women to find breast cancer risk. The results show contrast between pre- and post-menopausal women. In postmenopausal women high alcohol intake, greater weight, and greater BMI increased risk of BC. These data may be compared with those that examined these association and stratified by menopausal status. The findings are consistent, for example, with the reports of Hirose et al (1995; 2001) for weight and BMI (ORs: 2.05 and 3.60, respectively) or the previous data of Favero et al (1998) as well as the most recent study of Reinier et al (2007) for BMI (ORs=1.39 and 1.9, respectively).

The magnitude of positive association of the risk with BMI index ≥30kg/m^2 found in the current paper (OR=2.62, Table 2) was larger than that reported by Favero et al (1998) and Reinier et al (2007). The authors found no significant association between BC risk and BMI in premenopausal women similar as in the present study. In the literature on this subject, results for BMI were mixed (Carmichel and Bates, 2004). For example, Hu et al (1997) reported decreased risk of BC with BMI index for premenopausal women and statistically nonsignificantly increased risk (OR=1.98, 95% CI 0.86-4.55) for postmenopausal women. Obesity may be a significant contributory factor to the risk of postmenopausal BC by increasing concentrations of biological active estrogen resulting from conversion of androstendione, insulin and insulin-line growth factors (Friedenreich, 2001; Carmichel and Bates, 2004; McTiernan et al., 2006).

Family history of BC has been reported as being one of the strongest risk factor for BC (Claus et al., 1996; Hulka and Moorman, 2001; Antoniou et al., 2005). The present study also indicates the important role of family history of BC among first-degree relatives elevating the risk among pre- and post-menopausal women; the effect was greater for postmenopausal women. These results are relative consistent with those demonstrated by Reinier et al (2007), as well as by Hirose et al (1995, 2001), whereas Minami et al (1997) found a 3.5-fold increased risk of BC for women at age ≤49 years.

Among Polish women smoking prevalence is high. In the present study, both active and passive smoking elevated the risk in all women regardless of menopausal status. In contrast, Hirose et al. (1995) have not reported an increase in risk for tobacco smoking in postmenopausal women. In turn, Lissowska et al. (2006) using data from a large population-based case-control study in Poland found that passive smoking was not associated with BC risk, however the authors found increased relative risk for active smoking women at age <45 years (OR=4.39 for ever active compared to never active or passive smoking, and OR=1.95 for ever active vs never active smoking). Also increased relative risk of BC in case-control study (hospital controls, OR=1.28) was reported by Katsouyanni et al. (1994) among ever vs never-smokers. A recent collaborative reanalysis of 53 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 2002) focusing on smoking status concluded that cigarette smoking has no effect on overall risk of developing BC, but they indicated that a relationship in certain subgroups of women could not be excluded. In contrast, meta-analyses by Khuder et al. (2001) showed increased relative risk for ever-smokers (OR=1.10, 95% CI 1.02-1.18) and stronger association among premenopausal women. Also, Hu et al. (1997) found significant increased overall relative risk among ex- or current active smokers vs never smokers (OR=2.31, 95% CI 1.19-4.49).

Alcohol consumption has been shown to be a moderate but consistent BC risk factor (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). The Collaborative Group in their recent report (2002) concluded that women who reported intake of alcohol had increased the relative risk of BC compared with those who reported drinking no alcohol (e.g. OR=1.32, 95% CI 1.19-1.45 for an intake of 0.35-44g per day alcohol and OR=1.46, 95% CI 1.33-1.61 for an intake ≥45g per day, P for trend <0.00001). This study also indicates that intake

of alcohol is an important risk factor for BC, although alcohol consumption was low (mean ~1.2 drink/wk). The risk arising from consumption of alcohol was elevated in postmenopausal women consuming ≥2 drinks per week, OR=2.07, an increase was not clear in premenopausal strata. In contrast, Hirose et al. (1995) found a 2-fold increased risk in premenopausal women, and not clear relation among the postmenopausal. The main mechanisms that may be responsible for an induction of BC due to alcohol intake are discussed in a review by Dumitrescu and Shields (2005). The authors concluded that alcohol exerts influence on estrogen and folate metabolisms, gene regulation, and induction of mutagenesis.

A positive association between experience of psychological stress and BC risk was observed in both pre- and post-menopausal women in this study. The hypothesis that psychological stress is related to breast cancer risk has been widely discussed in several literature reviews (see, e.g. Bryla, 1996; Dalton et al., 2002; Kroenke and Kubzansky, 2005), but in a meta-analyses Petticrew et al. (1999) concluded that recent adverse life events are not causing factors for BC. The accumulation of the individual major life events, such as the death of a husband, divorce/separation, the death of a close relative, cancer in husband, child and other serious diseases of a family member during the 5 years before reference data appears to be approximately 1.6 times more likely to develop BC among participants of this study independently on menopausal status. This risk estimate is in accordance with several case-control studies (Ginsberg et al., 1996; Lillberg et al., 2003; Kruk and Aboul-Enein, 2004). For example, a large cohort study from Finland (Lillberg et al., 2003) have detected the risk increase related to major life events OR=1.35, 95% CI: 1.09-1.67). In turn, Jacobs and Bovasso (2000) observed that maternal death in childhood and chronic depression were associated with increased risk (ORs: 2.56 and 14.0, P<0.001, respectively). In contrast, several studies have not detected risk increases in relation to adverse life events (see Kruk and Aboul-Enein, 2004, and references cited therein). Hypothesized mechanism including of immune down-regulation, DNA damage, faulty DNA repair, effects on endocrine parameters, inhibition of apoptosis, or somatic mutation is proposed for the role of a stress in the BC etiology (Forlenza and Baum, 2000).

By using of OCP women are exposed to high concentration of estrogen, the hormone that promotes BC development. Data from the collaborative reanalysis from 54 epidemiological studies on the relation between BC risk and use of OCP provide strong evidence for a small transient increase in BC risk in current users compared with non-users (OR=1.24, 95% CI: 1.15-1.33) (Collaborative Group on Hormonal Factors in Breast Cancer, 1996), which disappeared 10 years after stopping (European Society of Human Reproduction and Embriology, 2004). In the present study, an increased risk of BC was observed among premenopausal users vs non-users (OR=1.65).

Prevalence of HRT use in Polish women is relative low but increases. According to findings by Rachon et al. (2004), based on data collected at the end of April 2002 among women aged 45-64 years, the prevalence of current HRT use was 12% and was dependent on women' education level. In this study, 37.8% cases and 39.0% controls were current or former users. These frequencies of HRT use are in line with recent results of Reinier et al. (2007). However, in the current study, the HRT users had no elevated BC risk as it was found, eg., in a study of Kamarudin et al (2006). There is a lack of total consistence among studies between exogenous hormones and BC risk (Hulka and Moorman, 2001). However, the Million Women Study (Million Women Study Collaborants, 2003) which examined British women aged 50-64 years demonstrated that current use of HRT was associated with increased BC risk (OR=1.66) and the effect was greater for estrogen-progestagen combinations use than for other types of the therapy. The study reported no BC risk increase for past users of HRT ≥10 years, OR=1.05). Also, Cuzick (2003) basing on quantitative estimates of the main risk factors reported a 2.3% increase per year for HRT use exceeding 5 years.

The recent research has put a special attention on consumption of red meat, as this product had been reported to increase the incidence of BC, colon and prostate cancers (Armstrong and Doll, 1975), and its consumption is popular in Poland. It is consistent with the findings of Liehr and Jones (2001). The authors had conducted a study on role of iron in induction of cancer and reported that excess iron absorption, in particular heme iron from meat or iron enriched food, contributes to the generation of reactive oxygen species. Also, a role of iron in estrogen induced cancer has been widely discussed by these authors. For participation of reactive oxygen species in steroidal estrogens metabolism to carcinogenic products see, for example, a recent review (Kruk and Aboul-Enein, 2006). Many of epidemiological studies have investigated the relation between red meat and fat consumption and BC risk, however the results are conflicting (Gerber et al., 2003; Gotay, 2005; Veronesi et al., 2005). In a pooled analysis of cohort studies representing 351 041 women (7,379 BC cases) Missmer et al (2002) found no significant association between BC and total or red meat consumption. Similarly, a pooled analysis of 8 prospective studies also failed to show any significant association between monounsaturated and polyunsaturated fat intake and BC risk (Smith-Warner et al., 2001). On the contrary, excesses of BC risk was reported for intake of animal fat from red meat consumption in the Nurses' Health Study II for premenopausal women (Cho et al., 2003). In turn, there are studies providing strong evidence that the high consumption of monounsaturated fat in the form of cold processed olive oil or seed oils was associated with reduced risk of BC (for the review and extensive discussion see Willett (2001). This effect is due to several biological functions, to increase of antioxidants concentration (Gerber et al., 2003). Moreover, observed in the present study increased risk in premenopausal women lends support to a positive relationship between red meat or animal fat consumption and BC risk.

There is some evidence that increased levels of vegetables and fruits intake may reduce the risk of BC.

To expand on these findings the association between fruit and vegetables intake and BC risk was examined. The current study supports an inverse association between high vegetables/fruits intake, and vitamin suplementation and BC risk in pre- and post-menopausal women. These data are consistent with findings of a number of past studies (reviewed in Willett, 2001; Temple and Gladwin, 2003; Key et al., 2004). Also Lissowska et al. (2007) in the most recent case-control study in Poland found significant associations between reduced overall BC risk and increasing levels of fruit intake (OR=0.76 for highest quartile vs lowest quartile), whereas, no evidence for total vegetable intake was found in both menopausal strata.

Moreover, the authors found that amplitude of the inverse association with fruit intake was dependent on BC subtypes. However, a pooled analysis of 8 cohort studies found no significant relationship between BC risk and the intake of vegetables and fruits (Smith-Warner et al., 2001). Still available evidence suggest that the diets of different populations might determine rates of BC and that low intake of fruits, vegetables and even moderate alcohol intake increase the risk of BC (Willett, 2001; Key et al., 2002). Therefore, finding of a protective role of the higher consumption of vegetables, fruit intake or vitamins supplementation in the current paper lends support to the role of these diet components as scavengers of oxygen reactive species participated in the process of steroidal estrogen metabolism to carcinogenic products. The association between metabolism of a carcinogen in breast tissues and risk of BC is poorly understood and further investigation of such relation is needed.

Scientific evidence indicates that physical inactivity is the most important known and modifiable risk factor for health. In 2002, the International Agency for Research on Cancer (IARC, 2002) concluded that the evidence on physical activity and BC prevention is strong and the most consistent thus overall level of evidence was classified as convincing. This study found that BC risk was inversely related to recommended levels of sports/recreational physical activity regardless of menopausal status. This finding is consistent with the most recent study of Kamarudin et al (2006). They found that inactive women had a significantly higher of BC risk (OR=3.489) compared to those who exercised regularly. Also, data from the California Teachers Study by Dallal et al. (2007) (110,599 women, 2,649 invasive and 593 in situ cases) also demonstrated a 20% reduction of the invasive BC risk among women practicing regular exercise >5 hours/wk per year. The authors observed a linear decrease in the risk with increasing amounts of exercise likewise as in the current study. Also, comparable in magnitude lower BC risk were found by Hirose et al. (1995) for both physical active pre- and post-menopausal women (ORs: 0.74 and 0.72, respectively). The biological mechanisms of the protective action of exercise against BC are poorly understood. The most frequently reported hypothesized mechanisms include decreased endogenous sexual and metabolic hormone concentrations, increased production of sex hormone-binding globulin, enhancing the immune and scavenging reactive oxygen species systems, and decreased obesity (Shephard et al., 1995; Dreher and Junod, 1996; Hoffman-Goetz et al., 1998; Yu and Rohan, 2000; Friedenreich and Orenstein, 2002; Jasienska et al., 2006).

Concerning reproductive risk factors, a significantly reduced risk of BC with increasing age at menarche was observed regardless of menopausal status in this study. This finding is consistent with results from previous case-control and prospective studies (Kampert et al., 1988; Kelsey et al., 1993; Hirose et al., 1995; Hu et al., 1997). Contrary to these observation, other study has found no association (Minami et al., 1997). The protective effect of late menarche may be due to shorted exposure of the breast to endogenous hormones.

The recent study also found the reduction in the risk for breast feeding among pre- and post-menopausal women. Studies on a relationship between lactation and BC risk are confounding. Several studies have found the reduction in risk in post- and pre-menopausal women, other studies have reported little or no relationship (reviewed in Kelsey et al., 1993). For example, the study by Kamarudin et al. (2006) reported decreased BC risk for breast-feeding in women who never use of OCP versus those never taking OCP and had not breast feeding (crude OR=0.435). In turn, Hirose et al. (1995) reported decreased BC risk among premenopausal women who had ≥6 months of breast feeding. Mechanisms postulated for the protective effect of breast feeding include the hormonal changes or physical effects in the epithelial cells (Kelsey et al., 1993).

In the present study a later age at first childbirth (≥30 years) increased overall BC risk after adjustment for age, breast feeding, stress experience and passive smoking ($p<0.002$) (data not shown). This finding agrees with the most common current view that women who experience their first pregnancy at older age (>30) are at increased risk than those who had their first childbirth before age 20 (Hulka and Moorman, 2001). Also, the most recent findings of Reinier et al. (2007) showed significantly elevated overall BC risk with a later age at first childbirth among postmenopausal women. Unfortunately, the current study was not able to find statistically important relation when women were stratified by menopausal status. This may be due to a small number of women who experienced the first pregnancy at age ≥30 years (5.3% all cases and 7.4% all controls). Additionally, the magnitude of the increase in BC risk reported in literature on this subject associated with a late age at first childbirth is modest.

Concerning parity, some studies have presented independent protective effect full-term pregnancies, while other research observed no additional protective effect after adjustment for age at first childbirth, as widely discussed in (Kelsey et al., 1993; Hu et al., 1997; Minami et al., 1997; Rieck and Fiander, 2006). In the current study an important protective effect of a parity was seen only among postmenopausal women having 1 or 2 delivery. These findings seems to agree with the previous studies showing that women at age ≥45 years having 2 children had a little decreased the risk (Kampert et al., 1988). On the contrary, other study Hirose et al., 2001) reported the protective effect of parity of a similar magnitude in premenopausal women, and decreased but nonsignificant

risk among postmenopausal women.

The present study, like all other case-control studies has certain limitations. One methodological issue was the selection of the non-cancer patients from ambulatories and hospitals as referents. To determine the discrepancy between these controls and the general population the control participants characteristics were compared with women surveyed by Chief Central Statistical Office (GUS) as the Polish Population Health Survey (GUS, 2006) and with characteristics of controls participated in a large population based case-control study in Poland (Garcia-Glasas et al., 2006) (2502 controls, mean age 55.9±10.1 years). The present study controls were found to have average number hours/week of recreational activity comparable to those women sampled by GUS, but they were more likely to be current smokers and abstinent than the general population (32.8% vs 23.1% and 45.2% vs 32.7% respectively). Comparing to controls in the Polish Breast Cancer Study (Garcia-Glasas et al., 2006) that evaluated risk factors by tumor characteristics, both groups of the control participants were very similar in terms of age, age at menarche, parity, age at first childbirth, age at menopause, family history, and current age. However, the current study controls were more likely to use OCP than those in the population-based study (14.6% vs 10.0%, respectively). Nevertheless, as the exposure of interest were based on self reports, therefore some recall bias cannot be ruled out in the current study. Also, misclassification of the exposure variables was possible due to self-reported measure or the assessment of lifetime history what relies on recall over long periods of time. However, such misclassification may be non-differential, since the same method was used to collect information from cases and controls. Moreover, this study measured only intake frequencies of dietary variables and was unable to adjust the calculated ORs for energy intake, and a control of body weight change through a women lifetime, that could confound the relationships. The study was also not free of response information bias to the questionnaire because all data were gathered after to BC diagnoses, and cases could be more aware of their lifestyle factors than controls. Nevertheless it is reassuring that ORs found in this study are on the whole within the range that reported by other authors. Nonetheless, this study did identify similarities and differences in BC risk profile for pre- and post-menopausal women.

Major strengths of this study are a large sample of cases and controls and its ability to provide for simultaneous description and analysis of several established risk factors for BC as well as those probable and possible. In addition, a dose-response relation over different levels of variables was examined in all analyses. Another major strengths were ability to carry out adequate adjustment for exposure to a broad range of potential confounders relating to reproductive, lifestyle, anthropometric risk factors and family history of BC. For example, for age at first childbirth the significant OR of 0.72 (adjusted for age) changed to 1.87 after adjustment for remaining risk factors significant in the final model, may be illustrative. A strength of the present study is also the restriction of cases to histologic confirmation of the disease. In addition, the response rate for eligible cases and controls was similar, what suggest that selection bias is not high.

In summary, the results obtained from this study provide additional evidence that reproduction-related factors like early age at menarche, late age at first childbirth, a lack of breast feeding, lifestyle factors (obesity, physical inactivity, smoking, alcohol intake, increased red meat and animal fat consumption, low vegetables and fruits intake, OCP use, experience of psychological stress), and family history of BC cancer are associated with elevated BC risk. The findings also suggest some differences in risk impact of some factors between pre- and post-menopausal women. The majority of the protective effects exerted by lifestyle factors identified in this paper are consistent with current recommendations by American Cancer Society for BC prevention (Kushi et al., 2006; Choices for Good Health: American Society Guidelines for Nutrition and Physical Activity for Cancer Prevention, 2007). A multifactorial process of the BC development, a tendency lifestyle variables to cluster, inconsistent and inconclusive data on BC risks coming even from a well-designed epidemiological research are the cause to continuously update knowledge on the risk factors with their impact on BC. This could help women to make changes in their behavior regarding diet and physical activity patterns that may reduce their BC risk. In this context it is also interesting that recent evidences suggest that more than 50% of cancer incidence could be prevented if a knowledge of risk factors would be applied to behavior changes (Colditz et al., 1996).

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