Epidemiologic Risk Factors for Breast Cancer Related to Menopausal Status in Indonesia

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Abstrak

Untuk meneliti faktor risiko <u>kanker payudara yang berkaitan dengan status menopause</u>, *dilakukan penelitian kasus kontrol pada rumah sakit di Indonesia. Pada 300 kasus dan 600 kontrol yang berpasangan menurul umur dan keadaan sosial ekonomi dilakukan wawancara . Kasus dan kontrol dikelompokkan berdasarkan status menopausenya dan dianalisis terpisah. Diperoleh temuan-temuan bermakna berikut ini.Di antara penderita kanker payudara pra menopause ditemukan peningkatan risiko pada yang mengalami trauma payudara (RR: 2,62; 95% JK: 1,09-6,31), menggunakan kontrasepsi oral (4,96; 1,51-16,24), mengkonsumsi susu (1,81; 1,01-3,35 konsumsi tiap hari versus nir konsumsi), makan buah sega r (2,42; 1,16-5,05, 3-4x per minggu versus kurang dari sekali per minggu). Penurunan risiko ditemukan pada wanita pengkonsumsi sayuran tiap hari (0,34; 0,15-0,77, konsumsi tiap hari versus tidak tiap hari). Di antara penderita kanker payuda ra pasca menopause ditemukan peningkatan risiko pada wanita dengan usia menard1e 15 tahun atau lebih (2,25·1,35-3,76), haid teratur setelah usia 30 tahun (4,61-· 2,45-8,67), konsumsi susu (5,84; 2,92-11,66, konsumsi tiap hari versus nir konsumsi). Penurunan risiko ditemukan pada wanita yang cerai atau janda (0,33; 0,18-0,58), jumlah melahirkan hidup atau bayi yang disusuinya tinggi (0,32; 0,13-0,76, menyusui 6 atau lebih bayi versus tidak menyusui).*

Abstract

To clarify the risk factors of breast cancer in premenopausal and postmenopausal women, a hospital-based case-control study was conducted in Indonesia. Three hundred inciden.t cases were inlerviewed and 600 controls were selected, matching for age and socio-economic class. Cases and controls were divided according to their menopausal status and analyzed separately. Following significant findi ngs were revea led. For premenopausal breast cancer, an increased risk was detected in women with breast trauma (adjus ted RR: 2.62; 95% Cl: 1.09-6.31), oral contraceptive u e (4.96,- 1.51-16.24), milk consumption (1.81; 1.01-3.35, daily intake vs no intake), fresh frui ts intake (2-42; 1.16-5.05, 3-4 times/week vs less than once/week intake). A decreased risk was detected in women with cooked-vegetable intake (0.34; 0.15-0.77, daily intake vs not daily intake). For postmenopausal breast cancer, an increased risk was found in women having menarche at the age of 15 years or over (2.25; 1.35-3.76), regular menstruation after thirty years old (4.61; 2.45-8.67), milk consumption (5.84; 2.92-11.66, daily intake vs no intake), and a decreased risk in women who were divorced or widowed (0.33; 0.18-0.58), and whose number of live birth or breast-fed children was high (0.32; 0.13-0.76, six or more breast-fed children vs no breast-fed child).

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Risk factors of breast cancer (BC) have been widely discussed, and different etiologic factors have been suggested related to menopausal status.[1-6] BC risk has been reported to be negatively associated with the number of pregnancies. This protective effect may apply only to women whose BC was diagnosed at 50 years or older.[7] A few studies suggest that parity may be associated with an increased risk of BC in young women.[8-9]

In postmenopausal women, body weight and other indicators of weight (weightlhe%ht ratio) were posi-tively associated with the risk, whereas in pre-menopausal women, a negative association has been reported between BC risk and weight.[11] BC risk in-

creased in first-degree rela tives of premenopausal BC patient, but not in relatives of postmenopausal BC patients.[3] Lactation showed protective effect against premenopausal BC alone.[3,6] The studies exemplified above strongly support the idea that premenopausal women differ from postmenopausal women concerning BC risk factors.

In view of the above differences, we have analyzed the risk factors in premenopausal and post menopausal women separately in this paper.

METHODS

Methodological details of the case control study design and data collection were already described in the preceeding paper. In this paper, cases and controls were grouped according to their menopausal status and were analysed separately. Relative risk (RR) with its 95% confidence interval (CI), computed as the exposure-odds ratio, was used as a measure of the associations between potentia l risk factors and BC. Trends were evaluated by the Mantel extension test.[12] To account for age, socioeconomic class, residence and other va riables potentia lly confounded, unconditional logistic regression analysis[13] was performed.

RESULTS

Out of 300 histologically diagnosed BC patients examined from December 1988 to November 1991 at Cipto Ma ngunkusumo Central Hospital, University of Indonesia, 135and 163patients were at premenopausal and postmenopausal status respectively. Two patients were at unknown menopausal status. The age distribution of cases and controls is shown in Table 1. Postmenopausal cases were significantly you nger than their controls (54.9 vs. 57.4 years old), whereas premenopausal cases were not significantly so (37.5 vs. 38.2 years old). Table 2 shows the mea n and standard deviation (SD) of height, weight and obesity indices as BMI and waist / hip ratio. In postmenopausal women, controls were significantly taller by 1.2 cm, and slightly smaller in waist / hip ratio than cases. Excl udi ng these differences, no other significa nt case-control differences were found in both premenopausal and post-menopausal study subjects.

Table 3 shows the RRs of breast cancer in premenopausal women obtained by univariate analysis. Breast trauma and the use of oral contraceptives significantly increased the risk. History of malignant neoplasm among relatives (mother, aunts or sisters) increased the risk by 91%, though the increase was not significa nt. The risk increased with increasing milk-intake and amount of fresh fruits consumed; significant linear trends were found (chi-squa re for trend = 4.83, $P<0.05$ and 4.68, $P<0.05$ respectively). Daily intake of cooked vegetables significantly decreased the risk.

Ta ble 1. Age Distri bution of Cases and Controls in Premenopa usa l a nd Postmenopa usal group

Age	Premenopausa l group				Postmenopausal group			
	Cases		Controls		Cases		Controls	
	Number	%	Nu mber	%	Number	%	Nu mber	%
20-29	14	10.4	30	<U				
30-39	60	44.4	163	49.5	10	6.2	4	1.5
40-49	59	43.7	124	37.7	33	20.4	31	11.4
50-59	2	1.5	12	3.7	52	32.1	115	42.4
60-69					58	35.8	107	39.5
70-79					9	5.6	14	5.2
Totals	135	100.0	329	100.0	162	100.0	271	100.0
Mea n age ± S.D.	37.5 "t f.i.4		38.2 j: 6.9 N S		54.9 ± 9.4		57.4 ± 7.6	

NS = not si gui fica nt, ▪ 0.05   p > 0.01

Table 2. Mean Values of Height, Weight and Obesity Indicators

	Premenopausal group				Postmenopausal group			
	Number	Means :I: S.D.			Number	Means :I: S.D.		
Height (cm)								
Cases	133	153.4	:I: 5.1	NS	161	152.3	:I: 5.2	
Controls	324	153.4	:I: 5.0		269	153.5	:I: 5.4	
Weight (kg)								
Cases	134	49.6	:I: 8.8	NS	161	50.8	:I: 10.6	NS
Controls	325	50.0	:I: 6.7		270	51.5	:I: 8.2	
Maximum weight (kg)								
Otses	94	52.8	:I: 7.8	NS	119	54.8	:I: 10.9	NS
Controls	223	52.5	:I: 7.9		211	55.5	:I: 8.6	
Waist (cm)								
Cases	133	70.0	:I: 7.9	NS	160	74.2	:I: 11.5	NS
C!ontrols	323	69.8	:I: 7.5		269	72.9	:I: 9.2	
Hip (cm)								
Cases	132	91.3	:I: 9.7	NS	161	94.1	:I: 13.3	NS
O.rntrols	323	91.5	:I: 9.1		270	95.0	:I: 10.6	
BMI (kg/m/m)								
Cases	133	21.0	:I: 3.3	NS	160	21.9	:I: 4.4	NS
nrntrols	325	21.2	:I: 2.7		269	21.9	:I: 3.2	
Waist / hip ratio								
Otses	132	0.77	:I: 0.09	NS	160	0.79	:I: 0.09	
Controls	321	0.77	:I: 0.09		269	0.77	:I: 0.09	

NS = not significant, ■ 0.05 2: p > 0.01,

Table 3. Distribution of Risk Factors in Premenopausal Group

Factors	Cases	Controls	R.R.	95% C.l.	Trend
Breast trauma					
Never	120	300	1.00	Reference	
Ever	15	13	2.88	(1.37 -6.07)	
Pill use					
No	126	324	1.00	Reference	
Yes	9	5	4.63	(1.67-12.84)	
Malignancy among relatives					
No	107	290	1.00	Reference	
Yes	19	27	1.91	(1.03 -3.54)	
Milk					
Never	38	98	1.00	Reference	4.83 *
Less than once/week	26	87	0.77	(0.43 -1.37)	
Once-twice/week	21	59	0.92	(0.49 -1.71)	
3-4 times/week	12	32	0.97	(0.45 -2.07)	
Daily	38	53	1.85	(1.06 -3.23)	
Fresh fruits					
Never - less than once /week	23	86	1.00	Reference	4.68 *
Once-twice/week	13	47	1.03	(0.48 -2.23)	
3.4 times/week	28	40	2.62	(1.36 --:- 5.05)	
Daily	71	156	1.70	(1.00 -2.91)	
Cooked vegetable					
Not daily	18	14	1.00	Reference	
Daily	117	315	0.29	(0.14 -0.58)	

0.05 2: P > O.Dl

Table 4. Distribution of Risk Factors in Postmenopausal Group

Factors	Otses	Controls	R.R.	95% C.I.	Trend
Marital status					
Married	86	95	1.00	Reference	
Separated or widowed	68 '	173	0.43	(0.29 — 0.65)	
Unmarried	9	3	3.31	(0.93 — 11.84)	
Height (cm)					
<1-SO	36	50	1.00	Reference	4.30
150 - 159	113	177	0.89	(0.54 — 1.45)	
i!: 160	14	44	0.44	(0.21 — 0.92)	
Waist /hip ratio					
< 0.70	28	65	1.00	Reference	5.53
0.70 - 0.79	57	101	1.31	(0.76 — 2.27)	
0.80 - 0.89	53	84	1.46	(0.84 — 2.56)	
i!:0.90	22	19	2.69	(1.27 — 5.67)	
Menarche					
< 15 years old	71	92	1.00	Reference	18.31t
i!: 15 years old	175	95	2.36	(1.60 — 3.50)	
Regularity of menstruation over 30 years					
Irregular	33	105	1.00	Reference	18.51t
Regular	130	165	2.51	(1.60 — 3.92)	
Menopausal process					
Natural	144	263	1.00	Reference	
Induced	19	8	4.34	(1.97 — 9.57)	
Number of live birth					
None	25	22	1.00	Reference	26.07 t
1, 2	44	35	1.11	(0.54 — 2.28)	
3-5	55	150	0.32	(0.17 — 0.61)	
i!:6	36	62	0.52	(0.25 — 1.03)	
Number of lactation					
None	29	27	1.00	Reference	28.83 t
1, 2	45	33	1.27	(0.64 — 2.53)	
3-5	56	153	0.34	(0.19 — 0.62)	
2: 6	31	57	0.51	(0.26 — 1.00)	
Smoking habit					
Nonsmoker	148	259	1.00	Reference	
Current ex-smoker	15	12	2.19	(1.00 — 4.72)	
Milk					
Never	54	138	1.00	Reference	32.20 t
Less than once /week	24	63	0.97	(0.55 — 1.71)	
Once-twice /week	20	27	1.89	(0.99 — 3.63)	
3-4 time , week	15	9	4.26	(1.85 — 9.81)	
Almost daily	50	33	3.87	(2.29 — 6.55)	

0.05 2: $P > 0.01$, O.Ql 2: $P > 0.001$, to.001 2: $P > 0.0001$

Table 4 summarizes the risk factors for post-menopausal women detected by univariate analysis. Compared to married women, separated or widowed women were at a smaller risk, but umnarried women were at a greater risk. When the marital status was dichotomized into unmarried and ever married, then unmarried women showed a RR of 5.22 (95% Cl: 1.58-17.21). Height was inversely associated with BC *(P<0.05),* while the larger the waist *l* hip ratio, the higher the risk *(P<0.05).* When compared to those with menarche at less than 15 years old, those with menarche at 15 years old or more had a higher RR. Regular menstruation after 30 years old and induced menopause increased the risk. Since the number of live birth and that of lactation showed very similar distribution, they showed similar RRs. When compared with nulliparous women, those with one or two births had a RR of 1.11 (0.54-2.28), 3-5 births 0.32 (0.17-0.61) and 6 or more births 0.52 (0.25-1.03); chi-square for trend being 26.07 (P<0.001). Similarly when compared to women with no breast-fed child, those with one or two breast-fed children had a RR of 1.27 (0.64-2.53), 3-5

children 0.34 (0.19-0.64) and 6 or more children 0.51 (0.26-1.00); chi-square for trend being 28.83 (P<0.001). Compared to nonsmokers, current or ex-smoker experienced a higher risk. Postmenopausal women who drunk milk less than once per week had a RR of 0.97 (0.55-1.71), once to twice per week 1.89 (0.99-3.63), 3-4 times per week 4.26 (1.85-9.81), almost daily 3.87 (2.29-6.55), when compared to non-drinker of milk; linear trend being significant (P<0.001).

After being adjusted for age, socioeconomic class, residence and other variables potentially confounded, by unconditional logistic regression analysis, the results (Table 5,6) were quite similar to those before adjustment. Association between BC with malignancy among relatives (premenopausal), height, waist *l* hip ratio, unmarried status, smoking habit and menopausal process (postmenopausal) became insignificant or marginally significant. The number of live births was not included in the logistic regression analysis, since its distribution was very similar to that of the number of breast-fed children.

Table 5. Adjusted Relative Risks of Breast Cancer in Unconditional Logistic Analysis in Premenopausal Group

Factors	R.R.	95% C.I.
Breast trauma		
Never	1.00	Reference
Ever	2.62	(1.09 — 6.31)
Pill use		
No	1.00	Reference
Yes	4.96	(1.51 — 16.24)
Malignancy among relatives		
No	1.00	Reference
Yes	1.99	(0.98 — 4.02)
Milk		
Never	1.00	Reference
Less than once/week	0.81	(0.42 — 1.54)
Once-twice/week	0.99	(0.50 — 1.95)
3-4 times/week	0.97	(0.42 -2.23)
Daily	1.81	(1.01 -3.35)
Fresh fruits		
Never - less than once/week	1.00	Reference
Once-twice/ week	0.70	(0.29 — 1.67)
3-4 times/week	2.42	(1.16 -5.05)
Daily	1.40	(0.74 -2.66)
O:ioked vegetable		
Not daily	1.00	Reference
Daily	0.34	(0.15 -0.77)

Table 6. Adjusted Rela tive Risks of Breast Cancer i n Unconditional Logistic Anal ysis i n Postmenopa usal Group

Factors	R.R.	95% C.I.
Marital status		
Married	1.00	Reference
Separated or widowed	0.33	(0.18 — 0.58)
Unmarried	2.71	(0.31 -23.63)
Height (cm)		
< 150	1.00	Reference
150 - 159	0.74	(0.40 1.36)
160	0.43	(0.17 — 1.13)
Waist / hip ratio		
< 0.70	1.00	Reference
0.70 - 0.79	0.99	(0.48 2.04)
0.80 - 0.89	0.44	(0.20 1.00)
0.90	0.81	(0.31 2.14)
Menarche		
< 15 years old	1.00	Reference
15 years old	2.25	(1.35 — 3.76)
Regularity of menstruation over 30 years		
Irregular	1.00	Reference
Regular	4.61	(2.45 — 8.67)
Menopa usal process		
Natural	1.00	Reference
Induced	2.54	(0.84 — 7.74)
Num ber of lacta tion		
None	1.00	Reference
1-2	1.15	(0.48 2.72)
3-5	0.29	(0.13 0.63)
6	0.32	(0.13 0.76)
Smoking ha bi t		
Nonsmoker	1.00	Reference
C'.urrent/ex-smoker	2.33	(0.76 — 7.09)
Milk		
Never	1.00	Reference
Less tha n once /week	1.13	(0.55 — 2.33)
Once-twice /week	2.26	(0.97 — 5.29)
3-4 ti mes /week	7.96	(2.63 -24.13)
Almost daily	5.84	(2.92 -11.66)

DISCUSSION

In the present study, we found the association between premenopausal BC and breast trauma, oral contraceptive use, high intake of milk and fresh fruits, and low intake of cooked vegetable.

Benign breast diseases have been reported as BC risk

factor,[11,14] but there have been no reports on the relationship between breast tra uma a nd BC risk. Therefore,   studies a re required to confirm such association.

Many reports noted that the use of oral contraceptives did not affect BC risk,[15-17] while our study revealed the contra ry. This might be due to the small number of

pill users in our series, thus our finding might possibly be obtained by chance. In the present study, mil k intake had positive association with BC risk and significa nt linea r trend was observed among both premenopausa l and postmenopausa l group. Milk might represent dietaR' fat which has long been incriminated for BC.

Protective effect of cooked vegetables might be due to the vitamins, such as vitamin A a nd beta-carotene, though inconsistent resu lts[20-22] were reported. The assoc1ation between fresh fruits intake and premenopausal BC might be related to the level of total calory intake.[23]

Associations between postmenopausal BC risk with ma rita l status, age at menarche, regula r menstruation

after thirty years old, induced menopause, number of live birth or breast-fed children and milk consumption were noted in this study.

Our study showed that unmarried women had 5.2 times higher risk than married women. Unmarried women had a higher risk, although some reports did not prove it.[5,24] The reason why separated or widowed women were at a lower risk of postmenopausal BC was unclear.

Menarche at older age was associated with postmenopausal BC in this study, but this is not a common finding.[11,25] Regular menstruation before menopause is known to be a risk factor of BC,[26,27] and our finding support this. Induced menopause was found to be a risk factor for postmenopausal BC by our univariate analysis, but not by logistic regression analysis. No risk difference was detected between natural and induced menopause.[28]

An inverse linear trend between postmenopausal BC and the number of live birth / breast fed children remained significant after adjusting for age and other factors in our study. Many studies[7,29,30] have reported that an increasing number of pregnancy or delivery has an independent protective effect. This protective effect was found more consistently in older or postmenopausal women. A few studies[8,9] suggest that parity may be associated with an increased risk for BC in young women. These are in good agreement with our findings.

Postmenopausal women who had smoking experience had approximately a two-fold BC risk in our study, however, this was not significant by logistic regression analysis. Most reports suggested no clear association between BC and cigarette smoking habits.[31,32]

CONCLUSION

Our study disclosed some different BC risk factors in premenopausal and postmenopausal women. We found more risk factors and stronger associations in postmenopausal than in premenopausal women. Milk intake was a common risk factor, which might represent fat intake.

Acknowledgments

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