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## LIFETIME MENSTRUAL ACTIVITY - INDICATOR OF BREAST CANCER RISK

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A case-control study of 67 cases of breast cancer and 157 controls was conducted to investigate the role of different behavioral, reproductive, and hormonal factors and to develop a unifying indicator of breast cancer risk. The results confirm previous reports of the influence of smearing on the risk of breast cancer. Age at menarche was found to be a risk factor among the premenopausal women. Late age at menopause was suggestive of an increase in risk. Long use of oral contraceptive or estrogen supplementation were risk-enhancing both pre- and postmenopausally. Lifetime duration of menstrual activity (LMA) combines age at menarche and menopause, parity, and lactation into a biologically plausible model. Our findings concerning LMA support its role as a determinant of breast cancer.

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### INTRODUCTION

Breast cancer is a leading contributor to cancer morbidity and mortality among women of Western industrialised countries, and its incidence is still rising (29). Although screening with mammography has proven effective in reducing mortality from breast cancer (45, 49), prevention of the disease can only be based on knowledge of the causal factors. Various hormonal, reproductive, dietary, and environmental factors have been investigated, but a coherent theory of breast cancer etiology fails to emerge from the accumulated data (2, 16). While unifying concepts are under scrutiny (9, 15), none has gained wide acceptance as yet.

The purpose of this study was to form a concept that would include the established hormonal and reproductive risk factors, as well as to investigate the influence of smoking on breast cancer.

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### SUBJECTS AND DATA COLLECTION

#### Cases

The eligibility criteria of the cases were: 1) age 35 to 69 years, 2) residency in the Helsinki Metropolitan Area, 3) any breast lump of clinical stage I or II, 4) nature (diagnosis) of the lump preferably not confirmed and told to the patient yet, 5) no previous cancer of any organ, and 6) interview able to be scheduled without delaying medical procedures.

The breast lump patients were nearly all (95%) recruited at seven clinics. Patients attending because of a breast lump were asked to participate. Those who, due to diagnostic procedures already performed, knew the nature of their breast lump were not approached. In most cases (75%) recruitment took place before the diagnostic procedures and thus without the woman knowing the nature of the lump. Those consenting to participate were given the background questionnaire at the initial contact, for completion at home.

Participants were studied as soon as possible after the initial contact. In most cases the interval was 1-2 days, and in all cases less than one week. In all, 224 breast lump cases were interviewed. Sixty-seven of these had a malignant tumor and 157 a benign tumor, as diagnosed subsequently.

### Controls

Community controls were selected randomly from the National Population Register. The same age and residency requirements were used as with the cases.

The controls were invited to participate by a letter describing the aims and procedures of the study, and asked the receiver to book an interview appointment. The invitation letter was accompanied by the background information questionnaire. If no reply was received within two weeks of mailing the invitation, a second letter was sent. Failing this, no other attempts were made to contact the woman.

The invitation letter was sent to 321 women. A total of 164 (51%) women attended the interview, while 57 (18%) declared reluctance or practical difficulties and 100 (31%) made no reply. Seven women were excluded from the final analysis because they had had cancer of the breast, uterus, or colon. Thus 157 (49%) women constituted the control group.

### Data collection

Cases and controls were interviewed by one of the three study nurses. During the interview visit, the nurse checked the questionnaire completed by the subject at home and made any necessary amendments. The questionnaire concerned demographic factors (type of residential area, education, occupation, marital status), as well as general medical, gynecological, family, and smoking histories. The nurse also asked additional questions concerning the diagnostic procedures, location of the breast lump and changes in symptoms.

Age at menarche was taken as the year when the first menses appeared. No attempt was made to gather details on the regularity or type of menses at their onset. Age at menopause was taken as the year the participant reported. Breast size was recorded as the cup size of bra usually worn by the woman. The four cup sizes were reduced to two breast sizes: small (A and B) and large (C and D).

Lifetime duration of menstrual activity (LMA) was calculated by taking the years from menarche to menopause (or to interview if premenopausal), subtracting nine months for each full-term pregnancy, six months for each lactation period, and adding the time of estrogen replacement therapy. In the case of hysterectomy without oophorectomy, the age at menopause was set at 48 years. The age at the time of oophorectomy was considered the age at menopause if no estrogen replacement therapy was given. The number of lifetime menstrual cycles (LMC) was calculated by taking the duration of lifetime menstrual activity (in years), multiplying it by 365 and dividing the result with the length of menstrual cycle (in days).

### Statistical analyses

Logistic regression models (3) were used to assess the effects of risk factors on the log odds of disease. First, linear trends of continuous variables were tested. For further analysis of certain variables the material was divided into tertiles, and cutting points were determined on the basis of the combined group of cases and controls. Odds ratios (OR) were calculated using the lowest tertile as reference group. Odds ratio confidence intervals were obtained by adding to the estimated regression coefficient plus/minus 1.96 times its standard error and then taking the exponential transformation of these values. Age was considered an important confounding variable and all relevant odds ratios were adjusted for age (treated as a continuous variable).

In addition to basing inference on odd ratios and their confidence intervals, differences in likelihood ratio statistics (deviances) were used to test the effect of omitting variables from the model. Assuming that the omitted variables have no effect, the deviance difference is approximately  $\chi^2$ -distributed with degrees of freedom equal to the number of omitted parameters (3).

When studying linear trends of variables that were not relevant for all women, such as age at first birth or years smoked regularly, an indicator variable was also included in the model. In the case of age at first birth this indicator variable took the value one for women who had ever given birth and zero for all others, thus taking care of any qualitative difference between these two groups. The linear trend for parity was thus confined to women with parity greater than 1.

## RESULTS

The characteristics of the cases and controls are presented in Table 1. Cases and controls did not differ from each other with respect to occupational classification of ten categories (data not shown).

There was a difference between pre- and postmenopausal women in the risk effect of age. Age increased, statistically significantly, the risk of breast cancer among premenopausal women by 11% for each year, whereas it was not related to the risk among postmenopausal women (Table 2). Late menarche was associated with an increased risk of breast cancer among premenopausal women, but an opposite, reduced risk was seen among postmenopausal women (Table 2). The odds ratio for age at menopause was suggestive of an increase in risk with late menopause. Age at first childbirth, parity, total lactation time, and length of menstrual cycle were not related to the risk of breast cancer in this study.

As Table 3 shows, large breasts were related to a reduced cancer risk before menopause. The regularity of menstrual cycles had an opposite effect on breast cancer risk around menopause, but the number of cases with irregular menstrual cycles was very small.

TABLE 1. - Characteristics of the study population.

Factor	Cases n = 67		Controls n = 157	
	Mean or %	(Sem)†	Mean or %	(Sem)†
Age (yrs)	54.7	( 1.0)	51.3	(1.1)
Age at menarche (yrs)	13.7	( 1.4)	13.5	(1.5)
Length of menstrual cycles (days)	26.4	( 0.5)	26.5	(0.2)
Parous (%)	65.7		77.7	
Parity (childbirths)	1.43	( 0.2)	1.61	(0.1)
Age at first birth (yrs)	25.5	( 0.6)	25.4	(0.4)
Total lactation time (mnths) <sup>a</sup>	8.27	( 1.6)	7.91	(0.9)
Menstrual breast tenderness (%)	80.3		70.7	
Age at menopause (yrs)	50.3	( 0.5)	49.4	(0.5)
Postmenopausal (%)	61.2		42.0	
Duration of menstrual activity (yrs)	35.6	( 0.8)	32.5	(0.7)
Lifetime number of menstrual cycles	481.4	(10.6)	456.0	(7.7)
OC users <sup>b</sup> (%)	25.4		29.3	
Use of OC (yrs)	5.4	( 0.9)	4.5	(0.5)
Non-OC <sup>c</sup> estrogen users (%)	43.3		28.7	
Use of estrogen (yrs)	7.2	( 1.2)	3.7	(0.6)
Bracup size (%)				
- small	60.0		54.8	
- large	40.0		45.2	
Smoking status (%)				
- never	53.2		67.5	
- ex-smoker	19.4		12.7	
- current	27.4		19.7	
Years smoked regularly <sup>d</sup>	20.9	( 1.8)	16.5	(1.3)
Number of cigarettes per day <sup>d</sup>	14.1	( 2.0)	13.6	(1.0)
Education (%)				
- primary school or less	50.0		51.0	
- junior high	27.4		24.8	
- senior high	22.6		24.2	
Socio-economic status <sup>e</sup> (%)				
- I	50.0		54.4	
- II	25.0		26.0	
- III	25.0		19.6	
Type of residency area (%)				
- rural	0.0		2.6	
- village	4.8		3.8	
- small town	3.2		3.2	
- city	90.3		89.9	
Family history of breast cancer (%)	0.0		6.4	

† Sem = Standard error of the mean;

<sup>a</sup> = ever lactated only;

<sup>b</sup> = OC = oral contraceptive;

<sup>c</sup> = Non-OC = estrogen replacement therapy;

<sup>d</sup> = Ever-smokers only;

<sup>e</sup> = Based on basic and higher education; I lowest, III highest.

TABLE 2. - Effect of age and hormone-related factors on the relative risk of breast cancer. The relative risks (odds ratios) are expressed per corresponding unit.

Factor	Premenopausal n = 117		Postmenopausal n = 106	
	OR †	95% CI*	OR †	95% CI*
Age (yrs) <sup>a</sup>	1.11	(1.01, 1.22)	0.98	(0.91, 1.04)
Age at menarche (yrs)	1.24	(0.91, 1.69)	0.87	(0.66, 1.16)
Age at first birth (yrs) <sup>b</sup>	1.01	(0.90, 1.13)	1.00	(0.89, 1.12)
Parity (childbirths) <sup>b</sup>	1.14	(0.64, 2.04)	0.89	(0.60, 1.32)
Total lactation time (mnths) <sup>b</sup>	0.97	(0.85, 1.09)	0.99	(0.95, 1.03)
Age at menopause (yrs)	-	-	1.10	(0.97, 1.24)
Length of menstrual cycle (days)	1.04	(0.87, 1.25)	0.97	(0.88, 1.08)

† Odds ratio adjusted for age;

\* 95% confidence interval;

<sup>a</sup> Unadjusted;<sup>b</sup> Adjusted for everparity (yes/no) also.

TABLE 3. - Breast size, menstrual cycle patterns, use of oral contraceptives and other estrogen, and the relative risk of breast cancer.

Factor	Premenopausal n = 117		Postmenopausal n = 106	
	OR †	95% CI*	OR †	95% CI*
Bracup size				
- large vs. small	0.31	(0.10, 1.01)	1.02	(0.46, 2.25)
Menstrual cycles				
- regular vs. irregular	0.59	(0.11, 3.19)	2.26	(0.63, 8.08)
Menstrual breast tenderness				
- yes vs. no	0.90	(0.30, 2.65)	3.45	(1.28, 9.32)
Use of oral contraceptives				
- less than 5 years vs. never	1.34	(0.48, 3.79)	0.72	(0.12, 4.42)
- 5 years or more vs. never	2.48	(0.61, 10.11)	2.21	(0.34, 14.54)
Use of estrogen supplementation				
- less than 4 years vs. never	1.47	(0.38, 5.71)	1.00	(0.23, 4.36)
- 4 years or more vs. never	1.98	(0.41, 9.66)	2.78	(1.02, 7.56)
Smoking				
- ever vs. never	2.01	(0.79, 5.11)	2.17	(0.90, 5.22)
- 15 years or less vs. never	0.96	(0.23, 3.96)	2.86	(0.80, 10.15)
- more than 15 years vs. never	2.95	(1.05, 8.31)	1.85	(0.67, 5.14)
Number of cigarettes/day				
- less than 15 vs. none	1.14	(0.35, 3.70)	3.20	(1.15, 8.90)
- 15 or more vs. none	2.58	(0.82, 8.08)	0.94	(0.24, 3.66)

† Odds ratio adjusted for age;

\* 95% confidence interval.

TABLE 4. - Lifetime duration of menstrual activity (LMA), number of menstrual cycles (LMC) and the relative risk of breast cancer.

Factor	Premenopausal			Postmenopausal		
	OR†	95% CI <sup>a</sup>	n*	OR †	95% CI <sup>a</sup>	n*
LMA (yrs)						
- 31	1.00		10/45	1.00		6/11
32 - 35	0.26	(0.07, 1.02)	8/31	1.23	(0.35, 4.29)	11/23
36	0.39	(0.05, 2.83)	8/15	1.95	(0.59, 6.43)	24/32
LMC						
- 419	1.00		7/43	1.00		10/13
420 - 495	1.46	(0.42, 5.07)	11/28	0.57	(0.17, 1.91)	9/27
496 -	1.16	(0.25, 5.33)	8/20	1.86	(0.61, 5.69)	22/26

† Odds ratio adjusted for age;

<sup>a</sup> 95% confidence interval;

\* Number of cases/controls.

Menstrual breast tenderness was a statistically significant indicator of increased breast cancer risk *after* menses had ceased altogether, i.e. postmenopausally.

Oral contraceptive (OC) use for five years or more brought about a two-fold increase in risk (Table 3). Use of estrogen supplementation for four years or more also doubled the risk of breast cancer. All the available parameters showed rather consistently that smoking is positively related to an increased risk of breast malignancy (Table 3).

Lifetime duration of menstrual activity (LMA) was first treated as a continuous variable, and the age-adjusted point estimates of odds ratios showed a 10% increase in breast cancer risk postmenopausally for each year of LMA (95% CI 1.02, 1.19). Premenopausally LMA was not related to breast cancer risk. Odds ratios for tertiles of LMA (Table 4) suggest a dose-response type of effect in the postmenopausal group. Among the premenopausal women tertiles of LMA showed just the opposite trend. As an attempt to refine LMA even further, we analysed the time of uninterrupted menstrual activity from menarche to either the first childbirth or, in the case of nulliparous, menopause. This part of LMA was not related to breast cancer risk.

Number of lifetime menstrual cycles (LMC) was not related to the risk when considered as a continuous variable. The point estimate of odds ratio was 1.00 for both the pre- and postmenopausal groups. Division of LMC into tertiles yields different results from LMA with respect to breast cancer risk. There was a suggestion of increase in risk with increasing number of menstrual cycles both pre- and postmenopausally (Table 4).

Lifetime duration of menstrual activity was studied more closely in relation to its principal components, menopausal status and age, in order to

characterize its validity as representative of the biological mechanisms effecting breast cancer risk. When LMA as a continuous variable was entered in a logistic model together with age, menopausal status and the interaction between age and menopausal status, the odds ratio for LMA still showed a 9% increase in risk (95% CI 1.01, 1.17). The deviance difference when excluding LMA from the model was 7.57 on 2 degrees of freedom ( $p < 0.05$ ). Note that with LMA excluded from the model the coefficients for age and menopausal status were significant. Inclusion of LMA made these coefficients smaller and insignificant. Thus it appears that LMA has a statistically significant effect on breast cancer risk independent of age and menopausal status, and that this effect absorbs the effect of these latter two variables. Inclusion of age at first childbirth, age at menarche, age at menopause as well as parity and estrogen use in the model did not alter these findings.

Smoking shortened the lifetime duration of menstrual activity. The mean LMA for cases who had never smoked, who had smoked for 15 years or less and who had smoked for more than 15 years was 37.3 years, 36.7 years, and 32.1 years, respectively. This was partly due to earlier menopause, since the age at menopause fell from a mean of 51.3 years among the never-smoking cases to 48.1 years among the longest smoking cases. A similar trend occurred among the controls.

## DISCUSSION

In this study the number of cases is relatively small. Even though the recruitment method was intended to gather almost all of the potential breast cancer cases, only a minority of all breast cancer cases were interviewed.

Based on the records of the Finnish Cancer Registry, 502 new cases of breast cancer in women aged from 35 to 69 years were discovered in the Helsinki metropolitan area during the recruitment period. Approximately 60% of these cancers were of clinical stage I or II. Thus, 22% of the potential cases were accrued for this study. The main reason for the poor recruitment rate was the rapidly growing number of private radiological clinics with practically no waiting list for mammographic examination, in contrast to the public hospitals which had waits of up to five weeks. Also, a large proportion of women were ineligible by having already undergone diagnostic procedures for their breast lump before coming to one of the recruiting hospitals. The possibility of a selection bias must therefore be carefully considered.

The age distribution of cases coincided with that of all breast cancer cases currently between 35 and 69 years of age (during the study period) and resident in the study area (E. Pukkala, Finnish Cancer Registry; personal communication). The residency distribution of cases was similar to that of all the breast cancer cases in the Helsinki metropolitan area (48).

Among the controls, comparison of women attending the interview with those who did not revealed no differences between the groups in residential district or in age. The community controls were thus representative as far as data permit us to determine.

Many aspects of life considered to be possible risk factors by the scientific community, including most of the characteristics of reproductive history, are not commonly recognized as such. Recall with respect to these factors should be the same among both cases and controls. By contrast, the odds ratios for those aspects of behaviour commonly regarded as unhealthy or suspect, such as smoking and oral contraceptive or estrogen use, should be interpreted more cautiously.

The hormonal and reproductive factors that have often been related to the risk of breast cancer can be viewed as indicators or signposts of certain biological phenomena. Events such as menarche, childbearing, lactation and menopause are of major importance in the *normal* physiological development and function of women. Early menarche, nulliparity, and late menopause should not be considered pathological *per se*. They can, along with other factors, be *related* to an increase or a reduction in the risk of breast cancer.

We believe that one of the true determinants of breast cancer risk that combines hormonal and reproductive factors is the duration of menstrual activity during a woman's lifetime. This has been proposed earlier (4, 51) and Korenman's much discussed "estrogen window hypothesis" also implies the idea (18). This phase of life begins with menarche and ends with menopause, each pregnancy (and lactation) shortening its duration. First birth interrupts menstrual cycles and the accumulation of uninterrupted "risk-time", rendering the structure of breast tissue less susceptible to the effects of hormonal fluctuations in the normal menstrual cycle

(1). If this is true, it can be argued that an even better determinant could be the total number of menstrual cycles during a woman's lifetime, since this takes account of the individuality of menstrual cycle length. This would be true if the accumulation of risk depends on the number of cycles only. On the other hand, if risk increases continuously during each cycle, the number of cycles would not be related to the risk as strongly as lifetime duration of menstrual activity.

We analyzed separately the importance of factors commonly recognized as relevant to the risk of breast cancer and contributing to lifetime duration of menstrual activity. Our data confirm the risk enhancing effect of early menarche (17, 20, 31, 32, 36, 37, 42, 52), but only in postmenopausal women; premenopausal women experienced a reduced risk. Similar findings have been reported (8, 14), but the reasons have evaded the investigators. Contrary to a number of previous works (6, 8, 17, 19, 25, 31, 32, 37, 44, 52) we found no association between age at first birth and breast cancer risk. In our study, the mean age at first birth was the same for cases and controls and the range of this parameter was rather narrow, giving little contrast. Parity has been shown to be either protective (8, 11, 21, 27, 36, 52) or to have no effect at all (30, 44, 46). The protective effect of parity has often been related only to high numbers of children (25, 31, 36). In this study there was no association for parity, which was quite low in both cases and controls.

In agreement with some earlier reports (4, 30, 44) there was no link between lactation and breast cancer risk. Compared to the studies from China (50, 52), the mean total lactation times in our study groups were far below the durations showing a protective effect.

The association between advancing age at menopause and breast cancer risk is widely accepted (11, 17, 20, 31, 32, 44, 46, 50), but most studies have used tertiles or other age-grouping in presenting the risk estimates, so that direct comparison with our results is difficult.

Menstrual breast tenderness has not been considered important in relation to breast cancer risk (47). The increased risk associated with this phenomenon in the present study suggests that it could be an indicator of unusually active breast tissue cells also susceptible to malignant changes later in life.

Use of oral contraceptives (OC) and use of estrogen for purposes other than contraception were both risk factors, but the effects were more obvious with longer usage. The mean times these two types of hormonal preparations had been used were short and the number of users was small. Results from earlier studies do not help evolve a coherent role for oral contraceptives or estrogen in the etiology of breast cancer. Several studies have found no association between OC use and breast cancer (40, 42, 43, 50), some have shown them possibly protective (10, 17, 46), and others have indicated a risk-increasing effect (28, 30, 36, 44, 52), which may be limited to current premenopausal users (26, 37). Estrogen use

also generates contradictory findings. Reports of the risk-lowering property of estrogens have found it to be weak (10, 17, 46). Earlier studies found short usage protective (32) or non-effective (7), but longer usage (five years or more) risk-enhancing (23).

Our findings concerning both the individual components of lifetime duration of menstrual activity and LMA itself support its role as a determinant of breast cancer. The difference between pre- and postmenopausal women in the effect of age on breast cancer risk suggests that when accumulation of LMA is continuing, age appears to be an important contributor to the risk. This is supported by the high correlation of LMA and age premenopausally. After menopause, advancing age has no effect on LMA and thus no risk-increasing effect of its own. That only very long LMA clearly increased the risk could mean a threshold effect. Najem and coworkers (30) have also reported risk-enhancement only with more than 30 years of LMA. LMA being protective premenopausally but risk-enhancing post-menopausally is suggestive of menopausal changes in the susceptibility of breast tissue cells to malignant changes. Further studies are needed to clarify this possibility.

The lifetime number of menstrual cycles (LMC) was, contrary to theoretical assumptions (12), not a better risk indicator than LMA. Determination of the individual LMC includes an estimate of *usual* cycle length. This estimate is subject to recall bias, which could increase with age (22, 34), affecting the odds ratios for LMC differently around menopause. Both regular and short menstrual cycles have been shown to increase breast cancer risk (20, 22, 34, 35, 52). However, older women tend to report shorter cycles (34) and recall menstrual irregularities less frequently (22) than younger women.

In our work, smoking reduced the age at menopause and so shortened the length of LMA. The protective effect of shortened LMA could counterbalance the risk-enhancement of smoking, but the odds ratios for different parameters of smoking remained high when adjusted for LMA. Hiatt and Fireman (13) reported a reduction in the age at menopause among smokers. When discussing the possible positive effect of this phenomenon in the risk, they conclude that it is clearly outweighed by the deleterious effects of smoking. Risk estimates range from 0.6 (33) to 4.6 (24), although more recent works rather uniformly suggested an enhancement of risk among smokers (5, 13, 24, 38, 39, 41), a finding which we verify.

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