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RISK FACTORS FOR BREAST CANCER AND THEIR PROGNOSTIC SIGNIFICANCE

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Abstract

Since 1960 a 50% increase has occurred in breast cancer incidence in Denmark. With the present rates one out of fifteen Danish women will develop breast cancer before the age of 75 years. To evaluate the influence of known and suspected epidemiologic factors on the risk of developing breast cancer and on prognosis, a population-based study has been carried out, where cases were identified from the files of the Danish Breast Cancer Cooperative Group (DBCG) and the Danish Cancer Registry. Results are communicated from the case-control part of this study, including 1486 breast cancer cases aged less than 70, diagnosed over a one-year period, and an age-stratified random sample of 1336 women without breast cancer from the general population. Data on risk factors were collected by self-administered (mailed) questionnaires. Classical risk factors, such as high social status, nulliparity, early menarche and late natural menopause were confirmed, while no association was found between breast cancer and maternal age at first childbirth.

Key words: Breast cancer, risk factors, case-control study.

With approximately 2500 new cases per year, breast cancer in the most common malignant disease among women in Denmark. The cumulative incidence rate is presently 6–7% or, in other words, one out of 15 Danish women will develop breast cancer before the age of 75 years.

Having remained constant from 1943, the incidence rate started to rise around 1960 and in 1982 a 50% increase had occurred. Part of the increase may be due to an increased awareness of breast cancer in the population as well as among doctors, though information on stage of disease, as reported to the Danish Cancer Registry, does not support a shift towards earlier stages (Table 1). It is interesting to note how the introduction in 1977 of the DBCG mastectomy procedure with axillary dissection changed the population-based stage distribution.

When changes in population size and age structure were accounted for by age-standardisation, the mortality rate from breast cancer remained virtually unchanged from 1943 to 1982 (6). It is, however, too early to evaluate any effect of the introduction of adjuvant chemotherapy on mortality in the population.

Previous epidemiologic studies have identified a number of risk factors for developing breast cancer, such as high social status, nulliparity, late age at first childbirth, early menarche, late menopause, obesity in postmenopausal women, previous benign breast disease and a family history of breast cancer. Other factors are suspected to influence the risk of breast cancer but their role is less well established. These include oral contraceptives, menopausal oestrogen therapy, high alcohol consumption and a high dietary fat intake (7). All these epidemiologic risk factors, supported by experimental and clinical evidence, point towards a hormonal aetiology of breast cancer. Although various hypotheses have been proposed to explain the biological mechanism, whereby oestrogen, progestogen or other hormones may be involved, none have so far proved satisfactory (7, 8).

In order to evaluate the influence of known and suspected epidemiologic factors on the risk of developing breast cancer and the prognosis, a population-based study was carried out in a collaboration between DBCG and the Danish Cancer Registry. This report presents results on social and reproductive factors from the case-control part of the study.

Material and Methods

The case group comprised 1694 women, aged less than 70 years, diagnosed with breast cancer between 1 March

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Table 1

Percentage distribution of stage of breast cancer as reported to the Danish Cancer Registry, 1963–1982

Stage	Year of diagnosis			
	1963–67 (n=8 375)	1968–72 (n=9 676)	1973–77 (n=11 306)	1978–82 (n=12 168)
Localised	66.8	72.9	69.1	50.4
Regional spread	19.7	15.3	17.9	34.1
Distant spread	9.0	6.7	7.7	8.3
Unknown	4.5	5.1	5.3	7.2

Table 2

Risk of breast cancer associated with demographic and social factors

Factor	Cases[a] n	Controls[a] n	Relative risk (95% CI)
Place of residence			
Capital	219	123	1.0 (R)[b]
Elsewhere	1 267	1 213	0.60 (0.47–0.78)
Married			
Ever	1 426	1 291	1.0 (R)
Never	60	45	1.15 (0.78–1.71)
Years of education[c]			
<8	587	590	1.0 (R)
8–12	546	475	1.12 (0.94–1.34)
13+	351	271	1.30 (1.06–1.60)
Social class[c]			
5 (low)	272	276	1.0 (R)
4	523	456	1.12 (0.91–1.39)
3	396	375	1.05 (0.84–1.31)
2	156	123	1.26 (0.94–1.68)
1 (high)	84	57	1.39 (0.95–2.04)

[a] Women with missing information on any particular factor are excluded.
[b] R denotes reference category.
[c] Risk estimates are adjusted for age and place of residence.

1983 and 29 February 1984. They were identified from notifications made by all Danish hospital departments to the DBCG and the cancer registry. As controls an age-stratified random sample of 1 705 women was drawn from the general population, identified from the Central Population Registry. Women with a breast cancer predating the study period were excluded from both case and control group.

Data on risk factors were collected by self-administered questionnaires identical for cases and controls. They were mailed to the cases one year after their diagnosis on a monthly basis. In order to achieve a similar procedure for controls, the preselected pool was divided into monthly batches which were assigned the same date of diagnosis as the cases. 1 486 cases (88%) and 1 336 controls (79%) completed the questionnaire. More controls (16%) than cases (7%) refused to participate, while more cases (3%) than controls (1%) were unable to respond due to illness or death. We did not manage to get in touch with 42 cases (2%) and 74 controls (4%).

Available information on date of birth, marital status and place of residence for all women in the study showed that non-responders were significantly older and more often single than responders, but there was no difference between cases and controls within the responding and non-responding group respectively. Regarding place of residence, however, cases were more likely to live in the capital than controls in both groups.

Comparisons between cases and controls for study factors were made by logistic regression techniques (3) using the statistical package GLIM (2) for the computations. The relative risk (RR), estimated from the odds ratio, was used as a measure of association. If the 95% confidence interval (CI) does not include the value 1.0, the RR is considered significant at the 5% level.

Results

The age distribution of cases and controls who completed the questionnaire was very similar, the mean age being 52.9 and 52.4 years respectively. Table 2 shows that women living outside the capital (Copenhagen), i.e. in Copen-

Table 3

Risk of breast cancer associated with reproductive characteristics

Factor	Categories	Cases n	Controls[a] n	RR (95% CI)[b]	p-value for linear trend in RR
Termination of 1st pregnancy	Full-term (28+ weeks)	1 142	1 116	1.0 (R)[c]	
	Early (−28 weeks)	166	110	1.43 (1.10–1.84)	
	Never pregnant	171	109	1.47 (1.14–1.90)	
Number of full-term pregnancies	1	217	185	1.0 (R)	
	2	568	505	0.98 (0.78–1.23)	0.01
	3	304	299	0.89 (0.69–1.15)	
	4+	177	221	0.71 (0.54–0.95)	
Age at 1st full-term pregnancy	<20 years	144	136	1.0 (R)	
	20–24	538	565	0.92 (0.71–1.20)	
	25–29	423	358	1.12 (0.85–1.48)	>0.5
	30–34	125	114	1.04 (0.74–1.78)	
	35+	25	29	0.77 (0.43–1.39)	

[a] Women with missing information on any particular factor are excluded.
[b] Relative risk (95% confidence interval), adjusted for age and place of residence.
[c] R denotes reference category.

Table 4

Relative risk (95% confidence interval) of breast cancer in relation to age at menarche, adjusted for age and place of residence

Age at menarche	Premenopausal (n=1 141)	Postmenopausal (n=1 556)
<13 years	1.0 (R)	1.0 (R)
13 years	1.26 (0.90–1.78)	0.90 (0.66–1.24)
14 years	0.93 (0.67–1.31)	0.85 (0.63–1.16)
15 years	0.64 (0.43–0.96)	0.78 (0.55–1.10)
16+ years	0.56 (0.35–0.90)	0.80 (0.57–1.14)
p-value for linear trend in RR	0.0006	0.13

hagen suburbs, provincial towns and rural areas, had a significantly decreased breast cancer risk. Consequently, subsequent risk estimates were adjusted for age, because this was a matching factor, and for place of residence.

Among a number of indicators of social status, 2 were more clearly related to breast cancer than others (Table 2). In relation to women with less than 8 years of education (primary school only), those with 13 years or more of education had a 30% excess risk. Social class was assessed on a scale made by the Danish Institute for Social Research (5), which takes into account occupation, job type, number of employees, and education. Women were grouped according to their own and their husband's class, which ever was the higher. Compared with those of low social class, women of the highest class had an increased risk, though the trend in risk was not significant from low to high social class.

The association between breast cancer and reproductive factors appears in Table 3. Women who had never been pregnant had a significantly almost 50% inceased risk compared to those whose first pregnancy lasted 28 weeks or more (in the following considered full-term). Early terminated pregnancies, i.e. before the 28th week, were also associated with an increased risk. This group was examined in more detail regarding the type of termination and outcome of subsequent pregnancies. If a woman never had a subsequent full-term pregnancy, an almost 3-fold increase in risk was observed (RR=2.83, 95% CI 1.32–6.07). Early terminated pregnancies in excess of one did not increase the risk further and small numbers made a distinction between induced and spontaneous abortions quite uncertain. No significant association was found between breast cancer and abortions in women who had a full-term pregnancy. In the latter group, there was a significant trend (p=0.01) of decreasing risk with an increasing number of full-term pregnancies (Table 3).

Contrary to many other studies, no relationship was demonstrated between age at first childbirth and breast cancer risk. Since women with many pregnancies may have started their childbearing earlier than those with few, a stratified analysis was performed. The risk reduction by 4 or more full-term pregnancies persisted after stratification for age at the first, while no consistent pattern was seen for age at first full-term pregnancy, 2 strata (parity 1 and 4+) showing no association and the 2 other strata (parity 2 and 3) trends in opposite directions. Similar analyses were carried out with other potentially confounding factors, such as age at diagnosis and place of residence, but the lack of association persisted.

Age at menarche was associated with breast cancer in premenopausal women only, where there was a highly significant trend of decreasing risk with increasing age at menarche (Table 4). Among postmenopausal women, the type of menopause did not appear to influence breast cancer risk (Table 5). However, no reliable information

Table 5

Risk of breast cancer in relation to menopause characteristics

	Cases n	Controls n	RR (95% CI)[a]	p-value for linear trend in RR
Type of menopause				
Natural	615	585	1.0 (R)[b]	
Surgical	189	170	1.14 (0.89–1.47)	
X-ray	4	4	1.05 (0.26–4.26)	
Other	14	12	1.04 (0.60–1.79)	
Unknown	14	15	–	
Age at natural menopause				
<40 years	11	17	1.0 (R)	
40–44	45	60	1.22 (0.52–2.88)	
45–49	185	193	1.53 (0.69–3.38)	
50–54	297	252	1.87 (0.85–4.10)	0.01
55+	56	40	1.97 (0.83–4.68)	
Unknown	21	23	–	
Age at surgical menopause				
<40 years	49	47	1.0 (R)	
40–44	41	48	0.75 (0.41–1.38)	
45–49	69	45	1.35 (0.75–2.43)	0.17
50–54	22	25	0.74 (0.35–1.57)	
55+	6	3	1.66 (0.38–7.29)	
Unknown	2	2	–	

[a] Relative risk (95% confidence interval), adjusted for age and place of residence.
[b] R denotes reference category.

was available on the extent to which oophorectomies had been performed in the group with a surgical menopause. A significant trend (p=0.01) was observed of increasing risk with increasing age at natural menopause, while there was no clear trend in risk for age at artificial menopause.

Discussion

The present study confirms the association between breast cancer risk and high social status. Previous studies have found higher risk estimates, but most of these were hospital-based where the controls may have been biased towards low social status and the risk consequently overestimated (4, 12, 17). Results from a recent Swedish study (16) agree well with the present, indicating that the true risk difference between the highest and lowest social group at least in Scandinavia is in the order of 30%.

Supported by occupational studies showing an increased breast cancer risk mainly in white collar workers and a low risk among blue collar workers (11), it seems that the relationship between breast cancer and social factors reflects life style rather than exposure to carcinogenic agents. Such life style factors include reproduction, which has been related to social status since women of high social status may tend to start childbearing at a later age and have fewer children. In this study, however, the overall association with social status was independent of reproductive variables.

The analysis of reproductive variables gave further evidence that full-term pregnancies protect against breast cancer. Women who never had one were at an increased risk and the risk decreased with an increasing number of full-term pregnancies. The increased risk associated with an early terminated pregnancy may be explained by the differentiation of the breast tissue which occurs late in pregnancy as opposed to the proliferation of breast cells which characterises early pregnancy (14).

The confirmation of parity as a protective factor and the lack of association between breast cancer and age at first birth agree well with large population-based studies from Sweden (1) and Norway (9, 10), but are at variance with many other studies (7). When the literature is reviewed carefully, bias arising from the design of the studies seems an unlikely explanation to this discrepancy. However, the possibility exists that determinants of age at first childbirth, such as relative infertility and family planning, may vary between populations.

Most studies, which have made a distinction between pre- and postmenopausal women, have found the protective effect of late menarche confined to the premenopausal group (12, 14, 15) as seen in this study. The lack of an effect of menarche on postmenopausal breast cancer risk may be due partly to unreliable recall in older women, partly to a diminishing effect with age (13).

Overall, this study showed no association between breast cancer and type of menopause. Since the data were self-reported, however, it was not possible to evaluate an effect of bilateral oophorectomy. The observed increase

in risk with a late natural menopause corroborates previous findings (7) and the lack of an association with age at surgical menopause was not surprising, because this group of women must be very heterogenous with respect to ovarian function.

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REFERENCES

1. ADAMI H.-O., HANSEN J., JUNG B. and RIMSTEN A. J.: Age at first birth, parity and risk of breast cancer in a Swedish population. Br. J. Cancer 42 (1980), 651.
2. BAKER R. J. and NELDER J. A.: The GLIM System Release 3. Numerical Algorithms Group, Oxford 1978.
3. BRESLOW N. E. and DAY N. E.: Statistical methods in cancer research. I. The analysis of case-control studies. IARC Scientific Populations No. 32. International Agency for Research on Cancer, Lyon 1980.
4. ELLERY C., MACLENNAN R., BERRY G. and SHEARMAN R. P.: A case-control study of breast cancer in relation to use of steroid contraceptive agents. Med. J. Aust. 144 (1986), 173.
5. ENEVOLDSEN B., MICHELSEN N., FRIIS-HASCHE E. and KAMPER-JØRGENSEN F.: Social classifications II. Svalastoga's subdivision according to social status rank and the social grouping employed by the Institute for Social Research. Ugeskr. Laeg. 142 (1980), 544.
6. EWERTZ M. and CARSTENSEN B.: Trends in breast cancer incidence and mortality in Denmark, 1943–1982. Int. J. Cancer 41 (1988), 46.
7. KELSEY J. L. and HILDRETH N. G.: Breast and gynecologic cancer epidemiology. CRC Press, Boca Raton 1983.
8. KEY T. J. A. and PIKE M. C.: The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. Eur. J. Cancer Clin. Oncol. 24 (1988), 29.
9. KVÅLE G. and HEUCH I.: A prospective study of reproductive factors and breast cancer. II. Age at first and last birth. Am. J. Epidemiol. 126 (1987), 842.
10. — — and EIDE G. E.: A prospective study of reproductive factors and breast cancer. I. Parity. Am. J. Epidemiol. 126 (1987), 831.
11. OLSEN J. H.: Occupation and risk of cancer in Denmark. An analysis of 93 810 cases, 1970–1979. Scand. J. Work Environ. Health 13 (Suppl. 1) (1987), 37.
12. PAFFENBARGER JR R. S., KAMPERT J. B. and CHANG H.-G.: Characteristics that predict risk of breast cancer before and after the menopause. Am. J. Epidemiol. 112 (1980), 258.
13. PIKE M. C.: Age-related factors in cancers of the breast, ovary, and endometrium. J. Chron. Dis. 40 (Suppl. 2) (1987), 59.
14. — HENDERSON B. E., CASAGRANDE J. T., ROSARIO I. and GRAY G. E.: Oral contraceptive use and early abortion as risk factors for breast cancer in young women. Br. J. Cancer 43 (1981), 72.
15. TALAMINI R., LA VECCHIA C., FRANCESCHI S. et al.: Reproductive and hormonal factors and breast cancer in a Northern Italian population. Int. J. Epidemiol. 14 (1985), 70.
16. VÅGERØ D. and PERSSON G.: Occurrence of cancer in socioeconomic groups in Sweden. Scand. J. Soc. Med. 14 (1986), 151.
17. VESSEY M. P., DOLL R. and SUTTON P. M.: Oral contraceptives and breast neoplasia. A retrospective study. Br. Med. J. 3 (1972), 719.