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## THE ASSOCIATION BETWEEN RISK OF BREAST CANCER AND AGE AT FIRST PREGNANCY AND PARITY IN MARIBO COUNTY, DENMARK

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### Abstract

The effect of age at first pregnancy and number of pregnancies was examined in a cohort of 14 421 women where reproductive informations were collected as part of a cervical cancer screening program. A total of 352 cases occurred in the cohort. In subgroups of women defined by age at first pregnancy the relative risk of breast cancer was lower among women who were first pregnant before 25 years of age (RR = 0.85 vs 1.20). In subgroups of women defined by parity the relative risk decreased with increasing number of pregnancies from about unity among women with 0–3 pregnancies to 0.7 among women with 6 or more pregnancies.

*Key words:* Breast cancer, reproductive factors, age at first pregnancy, parity.

Since 1970 numerous studies have shown an increasing breast cancer risk with increasing maternal age at first childbirth. Studies from Finland (1) and Iceland (2) supported this, though an additional protective effect of parity was found. Other Scandinavian studies have confirmed the effect of parity, but failed to demonstrate an association between age at first birth and breast cancer risk (3–6).

Since these factors affect the hormonal balance of a woman and thus are likely to influence the risk of breast cancer, we have investigated the association between risk of breast cancer and age at first pregnancy and parity, using a different study design than the previous Danish study.

### Material and Methods

In Denmark, screening programmes for cervical cancer have been conducted by the local health authorities on a county-wide basis. We were able to use the data collected as part of the cervical cancer screening programme in Maribo county to examine the risk of breast cancer in relation to parity and age at first pregnancy. The organis-

tion and effects of this particular programme on cervical cancer have appeared elsewhere (7). A brief description of details relevant for the present analysis is given in the following.

The study population comprised all women, born 1918–1939, who were living in Maribo county and thus were invited to the first cervical cancer screening round between 1967 and 1970, a total of 16 187 women. The screening programme included a PAP smear and a short interview on reproductive history, both carried out by a general practitioner. All women were registered by their personal identification number. In order to obtain a reproductive history as complete as possible, the data from the first screening round were supplemented by data collected in 3 subsequent rounds. Reproductive data were available from 14 421 women (89%). The interviews included questions on number of pregnancies and age at first pregnancy, but not whether the pregnancies continued to term, thus precluding an analysis of full-term pregnancies, which is the variable most commonly used in other studies. Out of the 14 421 women, 13 479 were 40 years or older when they were interviewed the last time. The cohort was followed up in the Central Population Register for death and emigration. Breast cancer cases in the cohort were identified by record linkage with the Danish Cancer Registry. In comparing the interviewed and non-interviewed women (Table 1), person-years at risk were accumulated from the date of the initiation of the screening programmes (September 11, 1967) until the date of diagnosis of cancer, emigration, death, or end of follow-up (December 31, 1984) whichever occurred first, whereas person-years at risk were accumulated from the date of the first interview when comparisons were made between the groups of interviewed women

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**Table 1**

*Relative risk for cancer 1967–1984 among interviewed and non-interviewed women invited to cervical cancer screening in Maribo county*

Site (ICD-7)	Interviewed n = 14 421			Non-interviewed n = 1 766		
	Obs	RR	95% CI	Obs	RR	95% CI
All	1 440	1.08	1.03–1.14	272	1.22	1.08–1.37
Breast (170)	307	0.86	0.77–0.96	45	0.78	0.57–1.04

**Table 2**

*Relative risk for breast cancer 1967–1984 among the interviewed women, by number of pregnancies*

Number of pregnancies	n	Obs	RR	95% CI
0	1 283	23	0.96	0.61–1.44
1	1 738	37	1.06	0.75–1.46
2	3 991	78	1.02	0.81–1.27
3	3 286	62	0.98	0.75–1.26
4	2 024	38	0.96	0.68–1.31
5	1 026	17	0.83	0.49–1.34
6+	1 036	15	0.70	0.39–1.16
Total	13 101	270		

Global  $\chi^2 = 2.66$ , DF = 5,  $p > 0.1$

Test for trend:  $\chi^2 = 8.23$ , DF = 1,  $p < 0.01$

**Table 3**

*Relative risk for breast cancer 1967–1984 among the interviewed women by age at first pregnancy*

Age at first pregnancy	n	Obs	RR	95% CI
<19	2 508	39	0.82	0.58–1.12
20–24	6 452	109	0.87	0.71–1.05
25–29	3 185	76	1.20	0.94–1.50
30+	956	23	1.20	0.76–1.78
Total	13 101	247		

Global  $\chi^2 = 7.04$ , DF = 3,  $0.1 > p > 0.05$

Test for Trend:  $\chi^2 = 0.91$ , DF = 1,  $p > 0.1$

Note: Cases diagnosed before the date of the first interview are excluded from the analysis, n = 37.

(Tables 2–4). Expected numbers were derived applying 5-year calendar and 5-year age specific incidence rates to the person-years at risk (8). Relative risk (RR) estimates were obtained from observed/expected ratios with 95% confidence intervals (CI), using an approximation to the Poisson distribution (9). Tests for homogeneity and linear trend were also performed (10).

### Results

A total of 352 breast cancer cases were observed in the cohort, 307 cases among the interviewed women and 45 among the non-interviewed.

Table 1 shows the observed and expected number of cancer cases, and the relative risk among interviewed and non-interviewed women. The overall risk of cancer was close to unity (1.08) among the interviewed women, and a little higher (1.22) among the non-interviewed women. The risk of breast cancer was lower than expected (RR = 0.86) among the interviewed women, and even lower (0.78) among the non-interviewed, thus reflecting the lower risk of breast cancer normally seen in rural areas in Denmark (11). Of the 307 incident breast cancer cases among the interviewed women, 37 occurred before the time of the first interview. These women were excluded from the analysis.

Tables 2 and 3 show the observed number of cases and the relative risk of breast cancer in subgroups of women defined by parity and age at first pregnancy. The risk gradually decreased as the number of pregnancies increased, from about unity for nulliparous women and women with one to four pregnancies, to 0.70 for women with 6 or more pregnancies. The trend in risk was statistically significant.

**Table 4**

*Relative risk for breast cancer 1967–1984 among the interviewed women, by age at first pregnancy and parity*

Number of pregnancies	Age at first pregnancy					
	Less than 25 years			25 years or more		
	Obs	RR	95% CI	Obs	RR	95% CI
1–2	48	0.78	0.58–1.04	67	1.35	1.04–1.71
3–4	74	0.99	0.78–1.24	26	0.93	0.61–1.37
5+	26	0.70	0.46–1.03	6	1.22	0.45–2.66

Nulliparous women were at the same risk as women with 3 to 4 pregnancies. The risk of breast cancer increased with increasing age at first pregnancy, from 0.82 and 0.87 among women with a first pregnancy before age 20 years and age 20–24 years respectively, to 1.20 among women who were 25 years or older when they were first pregnant. Rather than a risk gradient, there seem to be two different risk levels.

Table 4 shows the relative risk in subgroups defined by parity and age at first pregnancy. Although the pattern was not straightforward, the effect of parity did not seem to persist when controlled for age at first pregnancy.

### Discussion

Early age at first birth has long been regarded as an important protective factor for breast cancer. The International Collaborative Study found relative risks among women who gave birth at age 20 or below compared to nulliparous women from 0.26 (Tokyo) to 0.81 (Slovenia) (12). Later studies have found relative risks in the lower end of this range; Lilienfeldt et al. (13): 0.34 (age <20 vs nulliparous), Brinton et al. (14): 0.38 (age <20 vs nulliparous). In contrast, some studies from the Nordic countries have failed to demonstrate a protective effect of early first birth. Studies from Sweden (3, 15), Norway (5) and Denmark (6) have not been able to demonstrate a significant protective effect. However, an Icelandic study (2) found a relative risk of 0.27 among women with a first birth before 20 years of age compared to nulliparous women. A Finnish study (1) found a relative risk of 0.50 among women with a first birth before age 25 years compared to women who were 35 years or older when they first gave birth.

The reason for the differences between the Nordic studies is not obvious. Since negative and positive studies are of both case-control and cohort design, differences in design can probably not explain the findings. The two previous positive studies from the Nordic countries cover periods before the negative studies were performed. It is therefore possible that the importance of the protective effect of early first birth has changed in recent time. It is also possible that there are actual differences between the Nordic countries with respect to the relative importance of risk factors for breast cancer. The previous Danish study by Ewertz & Duffy (6), which found no effect of age at first birth, was based on breast cancer cases from the entire Danish population diagnosed in a one-year-period from 1983 to 1984. The present study, in which we found a 40% increase in risk among women whose first pregnancy occurred after the age of 25 (RR = 1.20, 95% CI = 0.97–1.46) compared to women who were pregnant for the first time before 25 years of age (RR = 0.85, 95% CI = 0.72–1.00), was based on breast cancer incidence in a cohort from a small rural part of Denmark, followed for a period

of 17 years. It is therefore possible that the diversity in findings can be explained by differences in study area or study period.

A protective effect of many births has been demonstrated in several studies. MacMahon et al. (12) found relative risks from 0.34 (Tokyo) to 0.90 (Slovenia) among women with 5 or more births compared to nulliparous women. In several subsequent studies relative risks below unity have been found: Lilienfeldt et al. (13): 0.44 (>4 births vs nulliparous), Paffenbarger et al. (16): 0.71 (>3 births vs uniparous). In some studies, for instance MacMahon et al., the effect of parity disappeared when controlled for other factors. In general, the Nordic studies have found a protective effect of high parity (1–4, 6). One study only was negative (15). In our study the protective effect of multiple pregnancies disappeared when controlled for age at first pregnancy. The diversity of findings in studies from the Nordic countries and the rest of the world might indicate that the relative importance of risk factors is not the same in all parts of the world.

The present study considers age at first pregnancy and total number of pregnancies, which is different from births. However, since most registered pregnancies terminate with the birth of a child, we believe that this has a limited influence on the results. This study was based on data already collected for other purposes, and since information on other potential risk factors for breast cancer was not collected, confounder control was not possible.

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