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BREAST CANCER IN DENMARK

Incidence, risk factors, and characteristics of survival

MARIANNE EWERTZ

In Denmark, incidence of female breast cancer remained constant from 1943 to around 1960, whereafter a steady increase has occurred, the level today being about 50% higher than in 1960. No equivalent rise has been observed for breast cancer mortality. Influence of hormonal and dietary factors on breast cancer risk and survival was evaluated in a combined population-based case–control and follow-up study, including 2 445 women, aged less than 70 years, diagnosed with breast cancer in Denmark between 1 March 1983 and 31 August 1984, identified from the files of the nation-wide clinical trial of the Danish Breast Cancer Co-operative Group (DBCG) and the Danish Cancer Registry. The control group was an age-stratified random sample of the general female population, selected from the Central Population Register. Data on risk factors were collected by self-administered questionnaires. Clinical and pathological tumour characteristics derived from DBCG. The case–control analysis confirmed an overall increased risk of breast cancer associated with urban residence, high social status, nulliparity, early age at menarche, late age at natural menopause, hormonal replacement therapy, high dietary fat intake, and high alcohol consumption in a subgroup. It failed to detect an association with age at first childbirth, oral contraceptives, smoking, intake of vegetables, tea, coffee, and sweeteners. Survival was determined by tumour size, skin invasion, number of positive lymph nodes, and grade. There was no relation between survival and reproductive or hormonal factors, dietary variables, alcohol consumption, or smoking. However, a complex relationship may exist between survival and body mass index.

Breast cancer (BC) is the most frequent malignant disease among women worldwide. It was estimated that 572 100 new cases were diagnosed worldwide in 1980, accounting for about 18% of all cancers in women (1). In developed countries, BC generally represents between 15 and 20% of all cancer deaths among women and 2–5% of all deaths (2). BC is, therefore, an important public health problem.

There is substantial international variation in BC incidence, the rates in Northern America and Northern Europe being almost 10 times higher than those in China and certain parts of Africa (1, 3). Studies of European migrants from low incidence areas (e.g. Poland and Italy) to high incidence areas, such as USA, Australia, and Israel, show that the BC rates approach those of the new host country within the life-span of the migrating women (4–7). This suggests that environmental factors in the broadest sense play a major role in the aetiology of BC.

Epidemiological studies have identified a number of factors which influence women's risk of developing BC. These can be divided into 3 main categories. The first relates to female sex hormones and includes endogenous factors which increase the risk of BC, such as early age at menarche, late age at natural menopause, late age at first childbirth, and none or few childbirths, and exogenous factors, i.e. administration of female sex hormones as oral contraceptives or menopausal replacement therapy (8). The role of the latter as well as other aspects of reproduc-

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From the Danish Cancer Society, Division for Cancer Epidemiology, Strandboulevarden 49, Box 839, DK-2100 Copenhagen Ø, Denmark.
Correspondence to: Dr Marianne Ewertz, address as above.

tion, e.g. early terminated pregnancies, sequencing of births, and lactation, remains to be clarified (2). The second category comprises various life-style factors, such as diet, alcohol consumption and smoking, which have been suggested to be associated with BC risk. However, studies of particularly diet have yielded inconsistent results. Other risk factors can be grouped together in a third category. This includes socio-economic status, family history of BC, benign breast disease, previous breast or endometrial cancer, and ionizing radiation exposure. Of all risk factors examined, only radiation has a documented causative effect. Yet it is clear that only a minor fraction of BCs can be ascribed to radiation exposure. More knowledge about BC aetiology and associated risk factors is required to reduce BC morbidity through primary prevention.

The prognosis after BC is determined primarily by stage of disease, but evidence of other factors which might affect the course of the disease is relatively sparse. Factors, which increase the risk of developing BC and thus presumably somehow affecting the growth of malignant breast cells, might continue to influence the growth of malignant cells not eradicated by primary treatment and thus the prognosis. The identification of new prognostic factors might lead to improvements of the treatment of BC.

With more than 45 years of population-based cancer registration, the Danish Cancer Registry offers data to study long-term trends in BC incidence. Since 1977, the Danish Breast Cancer Co-operative Group (DBCG) has coordinated the diagnosis and treatment of BC in Denmark. In a collaboration between the Danish Cancer Registry and the DBCG, a combined case–control and follow-up study was conducted with the aim of elucidating the influence of social, reproductive, hormonal and dietary factors on BC risk and survival. This report is a synopsis of our findings.

Breast cancer incidence and mortality

Material and methods

Since 1942, the Danish Cancer Registry has registered all cases of cancer occurring in the entire Danish population. The registry is regarded as virtually complete. Details of the Danish cancer registration have been published elsewhere (9).

From 1943 to 1987, close to 80 000 incident cases of female BC were notified to the cancer registry. A detailed analysis was performed including 65 870 cases diagnosed in women aged 25 years or more between 1943 and 1982 (10). All histologic types of invasive cancer were included, whereas pre-cancerous or in situ lesions were excluded. The proportion of histologically verified tumours ranged from 83% in 1943–1947 to 95% in 1978–1982. Corresponding figures for those known to the registry by death certificate only were 8.8% and 0.6% respectively.

The number of women with BC as the underlying cause of death was abstracted from the annual publication 'Causes of Death in the Kingdom of Denmark' issued by the National Board of Health. This material included a total of 40 111 deaths from 1943 to 1987.

All BC rates were calculated as average annual rates per 100 000 women with the Danish female population at risk in the period as denominator. Age-standardization to the world population was performed by the direct method (3). Statistical models of the multivariate Poisson type were applied to estimate separate effects of age, calendar time of diagnosis, and birth cohort (11).

A similar analysis was carried out for BC in males, but due to the low disease frequency, the study population was expanded to include 3 other Nordic countries, Finland, Norway, and Sweden (12). The material comprised a total of 1 529 cases of male BC, diagnosed from 1943 to 1982. Between 90 and 96% were histologically verified and a maximim of 3.4% ascertained from death certificates only. In the comparison between countries, the cumulative incidence rate, age 0–74 years, was used (3).

Results and comments

The incidence of female BC in Denmark remained constant from 1943 to around 1960, whereafter a steady increase has occurred, the level today being about 50% higher than that around 1960 (Fig. 1). Currently, the cumulative incidence rate, age 0–74 years, is 7.4%, or in other words, approximately 1 out of 14 Danish women will develop BC before the age of 75 years.

The incidence of BC is higher in the capital (Copenhagen) and surrounding suburbs than in provincial towns and rural areas (Fig. 2). The difference between the capital and its suburbs has disappeared with time. In the other areas the time trend has been similar to that in the capital and the difference between the areas remains. In 1983–1987, the cumulative incidence rate, age 0–74 years, was

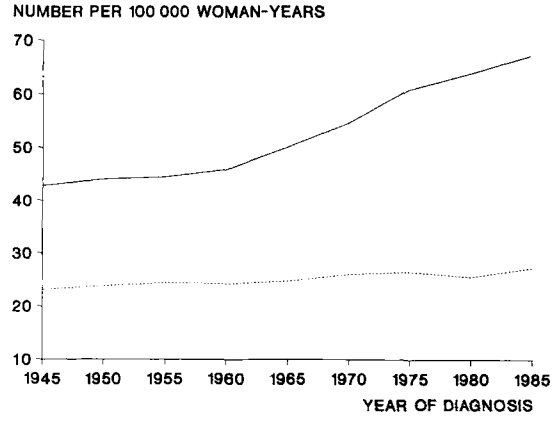

Fig. 1. Age-standardized (world population) incidence (——) and mortality (.....) of breast cancer in Denmark, 1943–1987.

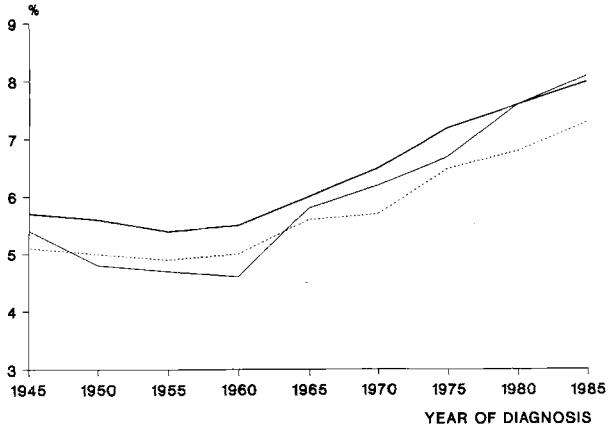

Fig. 2. Regional variation in cumulative incidence rate, age 0–74 years, of breast cancer in Denmark, 1943–1987. —— capital; —— suburbs; – – – – provincial towns; ..... rural areas.

8.0%, 7.3% and 6.7% for the capital, provincial towns and rural areas respectively (Fig. 2).

The statistical modelling confirmed a significant effect of calendar time on BC incidence, but indicated that the increase in BC incidence was due mostly to an effect of birth cohort. Compared with women born in 1858, the BC risk rose slightly up to the turn of the century, whereafter a more marked increase occurred, the risk being approximately 3-fold higher for women born around 1950 than for those born around 1900.

The examination of age on BC incidence demonstrated clearly the well-known 'Clemmesen's hook' (13), the rates

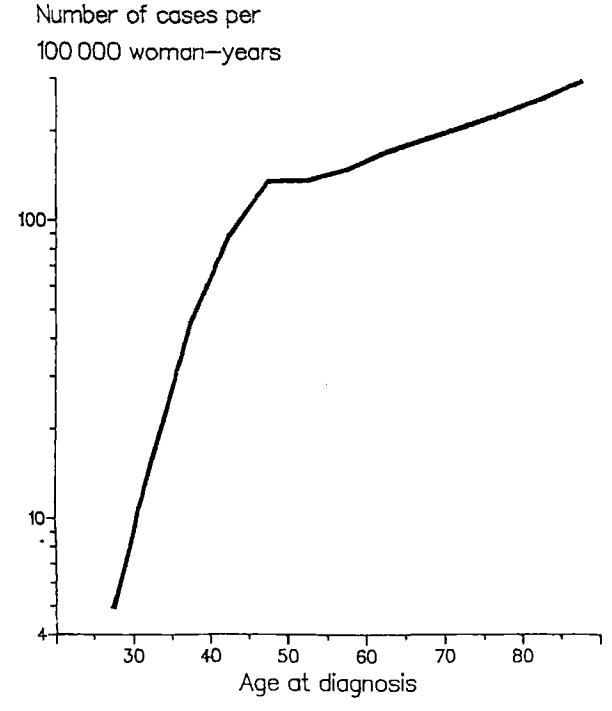

Fig. 3. Age-specific incidence of female breast cancer in Denmark, 1943–1982 (10).

rising up to around age 50, then levelling off (the hook), to resume an increase with a different slope after the age of 55 (Fig. 3).

While the incidence has been increasing, the mortality rate from female BC has remained almost constant from 1943 to 1987 (Fig. 1). An examination of mortality rates by birth cohort revealed no systematic difference between cohorts born 1868–1947.

An increase in incidence without a corresponding rise in mortality is also seen in other countries in Europe and in the USA. In the absence of bias related to cancer or death registration, this can be interpreted as an improvement in survival, achieved through earlier diagnosis and more effective treatment. Adjuvant chemotherapy to node positive patients was introduced in Denmark by the DBCG in 1977. The relative gain in mortality reduction from such therapy lies in the order of 15–35% (14). However, this improvement is not sufficient to explain the entire difference between incidence and mortality, and data from the Danish Cancer Registry do not show an increasing proportion of early stage BCs with time (10). It is therefore possible that an increasing diagnostic effort over time against breast lumps may have led to the detection of tumours which are histologically malignant, but biologically benign (15).

BC is a rare disease in males, accounting for only about 1% of all malignant breast neoplasms. In Denmark, on average 18 new cases were notified per year in 1983–1987. While a consistent time trend was observed for female BC incidence in the Nordic countries, the incidence of male BC varied much more with no clear trend with time (Fig. 4). No consistent pattern was found for birth cohort.

The effect of age on male BC incidence was best described by:

$$I(age)^k = b(age)$$

i.e. a straight line when the logarithm of incidence was plotted against the logarithm of age. Fig. 5 shows this plot, illustrating the difference between the four Nordic countries, the slopes (k) varying between 4.5 (Finland) and 5.4 (Denmark).

There are many similarities, clinically and histologically, between BC in males and females (16, 17) to suggest that BC is one disease entity. Clues to the aetiology may therefore be obtained from a comparison of the characteristics of the disease in males and females. Comparing the incidence of male and female BC, the sex ratio is the most striking, BC being about 100 times more frequent in females than in males (Fig. 4). Secondly, the age-specific incidence curves differ. In males, incidence (Fig. 5) as well as mortality (18) increases in a linear fashion with the logarithm of age with a slope of 4.5–5.4, thus resembling other epithelial tumours (19). In females, however, the age-specific incidence curve can be resolved into 2 components with different slopes (Fig. 3). The slower rate of

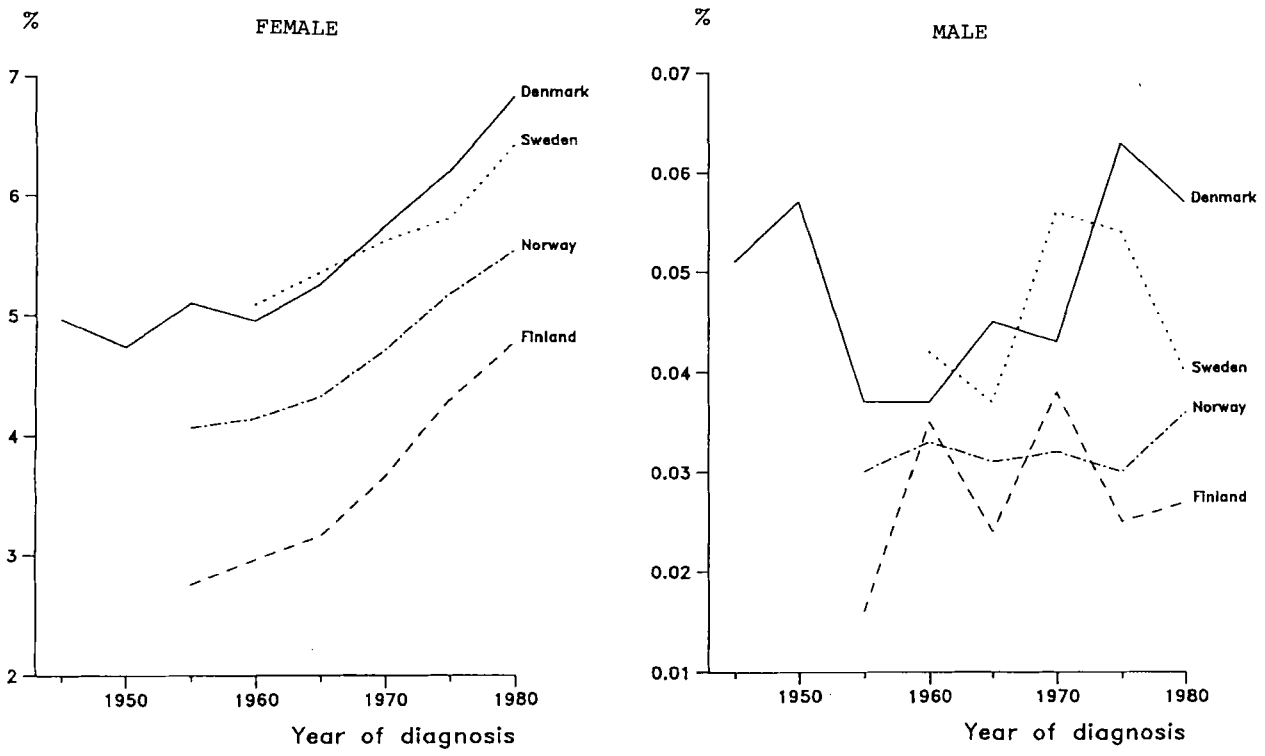

Fig. 4. Cumulative incidence rate, 0–74 years, of breast cancer in Denmark, Finland, Norway, and Sweden, 1943–1982 (12).

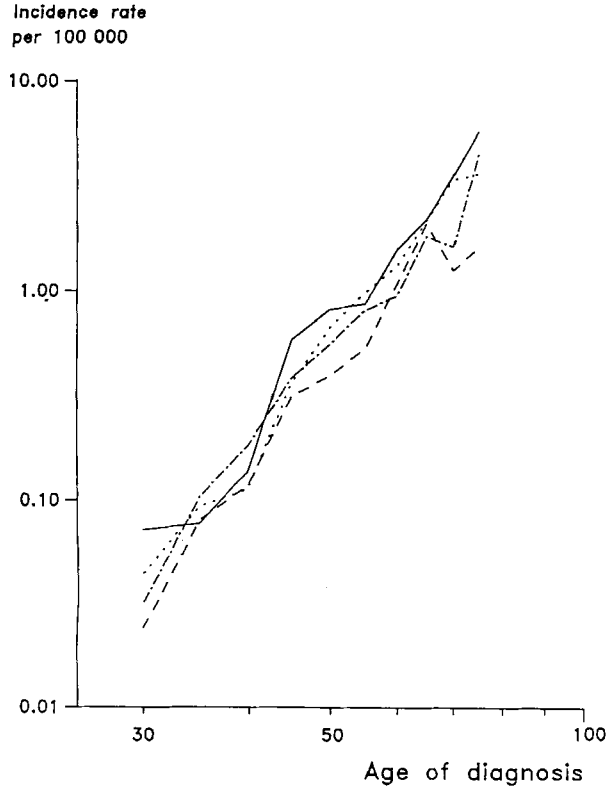

Fig. 5. Age-specific incidence of male breast cancer in Denmark (——), Finland (– – – –), Norway (– · – · –), and Sweden (· · · ·), 1958–1982 (12).

increase after the age of 50 years may be interpreted as a cessation of exposure to a carcinogenic agent. Clemmesen (20) suggested a protective effect of menopause, which was later elaborated by Pike (21), who predicted that the incidence by age 70 would be 4-fold increased, if women continued to menstruate into old age. Thus, the sex ratio and the age-specific incidence curves point towards an involvement of female sex hormones in the aetiology of BC. This is supported by ample evidence from animal, epidemiological and clinical research (8).

Finally, the international variation in BC incidence is similar for males and females (3). This was also the case within the Nordic countries (Fig. 4), providing further evidence of BC being one disease with common aetiological factors involved in males and females. Case–control studies of male BC (22–27) have generally failed to identify such common aetiology factors. While diet has received much attention in relation to the international variation in female BC (28), no data are presently available on the role of diet in relation to BC in males.

Conclusion

Descriptive epidemiological data suggest that two sets of aetiological factors are involved in the development of BC. The first set of factors is related to female sex hormones and may explain the sex ratio and age-specific incidence curves of male and female BC. The second one may be common

for both male and female BC and may explain the component of the international variation not accounted for by the first. However, the second set of aetiological factors remains to be established.

Risk factors for female breast cancer

Material and methods

Cases. The case–control and follow-up study was designed to include all women, aged less than 70 years, diagnosed with BC in Denmark between 1 March 1983 and 31 August 1984. They were identified from the files of the DBCG and the Danish Cancer Registry. A total of 2 705 cases were identified. Case ascertainment and data collection were delayed till one year after the diagnosis to allow for delays in notifications to the DBCG and the cancer registry as well as to avoid asking questions on diet during a period, where adjuvant chemotherapy was administered, with the recognized side-effects (nausea, vomiting). During this one-year delay, 123 patients died. At the end of the study, the case file was checked against the databases of the DBCG and the cancer registry for completeness. Fourteen patients were notified after the completion of the study and thus not included. Furthermore, 40 cases were excluded due to a BC predating the study period. The BC diagnosis was histologically confirmed in all but five cases. In situ cancers, a total of 83, were included in the analysis of incidence risk factors, but excluded from the analysis of survival.

Controls. The control group was an age-stratified random sample of the general female population, selected from the Central Population Register (CPR). Established in 1968 with the purpose of storing commonly used personal data for each inhabitant and acting as source material for the administrative systems in Denmark, this register constitutes a complete sampling frame for the entire population. The key identifier is a 10-digit ID-number, the first 6 digits being the date of birth. The register is a computerized and updated on a regular basis. Through a linkage with the Danish Cancer Registry database, controls with a BC predating the study period were excluded.

Data collection. Data on risk factors were collected by self-administered questionnaires 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. If a questionnaire was not returned within 6 weeks, or was grossly incomplete, the woman was contacted by telephone. By this procedure, non-responders were approached automatically and their reason for lack of response sought. The telephone contacts were conducted by the author and two trained secretaries, who were responsible for the administration of the questionnaires. During data collection and processing, the study personnel was blind to the women's status as cases or controls. Other data were derived from computer-based record linkages using the personal ID-number as a key identifier. Information on demographic variables, such as age, area of residence, and marital status was available from the CPR for all women in the study. Area of residence was categorized from municipalities into four groups, the capital (central Copenhagen), suburbs around Copenhagen, provincial towns, and rural areas according to the population density in each municipality.

Assessment of risk factors. Social status was evaluated by years of education, employment status, type of job, branch of occupation, type of husband's job and social class. The latter was scored in accordance with a scale from the Danish Institute for Social Research, taking into account the aforementioned variables (29). For women who had ever been pregnant, the year of termination of each pregnancy was recorded as well as the outcome (induced abortion, miscarriage, or childbirth). In the case of early terminated pregnancies, the month of termination was recorded. Due to the one-year lag between diagnosis and data collection, corrections were made to adjust menopausal status, age at menopause, and variables related to usage of oral contraceptives (OC) and other sex hormones to the status at diagnosis (or equivalently for controls). Information on use of sex hormones included age at start and end of treatment, total duration, and ordered duration of up to 6 different brands of OC and 5 different brands of other sex hormones, but no dose for the latter. To help in recall, the questionnaire contained lists of 64 brand names of OC and 55 brand names of other sex hormones, mainly used for the alleviation of menopausal symptoms. Anthropometric measures included self-reported height and current weight, as well as weight 10 and 20 years prior to diagnosis and at age 20. The body mass index (BMI) was calculated as current weight divided by height squared. The dietary part of the questionnaire was of the semi-quantitative food-frequency type, designed specifically to estimate the women's usual intake of fat, beta-carotene and alcohol. A list of 21 food items were constructed, covering about 80% of the consumption of fat, beta-carotene, and alcohol in the study population. Additional questions addressed the intake of tea, coffee, sugar, artificial sweeteners and dietary supplements, e.g. vitamins. Subjects indicated how often they consumed each item under headings of per day, week, month, or never, the latter being described as less than once per month. Portion sizes were illustrated by color photographs. The calculation of nutrient intake (total fat, beta-carotene, and ethanol) from the items included in the questionnaire has been reported in detail (30). Unfortunately, the questionnaire was not designed to evaluate total energy intake, since the importance of this variable became evident only after the completion of this study (31).

Questions on smoking elicited information on past and current smoking, age at starting and stopping, duration, preferred type of tobacco (cigarettes, cigars, pipe), and amount smoked per day. The smoking variables were also corrected for the one-year lag between diagnosis and data collection. Cigarette-years of exposure (number of cigarettes per day multiplied by duration) was calculated as a summary variable.

Analysis. The study was designed to generate 2 datasets for the analysis of risk factors of developing BC:

1. The role of risk factors, excluding OC use in women aged less than 40 years, was addressed for incident BC cases diagnosed over a one-year period (1 March 1983–29 February 1984) and corresponding controls.
2. The association between OC and BC risk was examined separately for women diagnosed with BC under the age of 40 years over an 18-month period (1 March 1983–31 August 1984) and corresponding controls.

Obviously, the 2 datasets were overlapping. The measure of association between study factors and BC was the relative risk (RR) estimated from odds ratios. Comparisons of cases and controls were made by unconditional logistic regression techniques (32), using the statistical packages GLIM (33) and EGRET (34) for the computations. Risks were considered significantly different from base-line risks if the 95% confidence interval (CI) excluded the value 1.0. Adjustment for the effect of other factors was performed, where necessary, including tests for interaction between study factors. In the case of ordered variables, significance was also evaluated by testing for a linear trend in RR. Since cases and controls were frequency matched on age, all RR-estimates were adjusted for age.

Response rate. A total of 1 694 BC cases diagnosed over a one-year period and 1 705 controls were invited to participate in the main part of the study (dataset 1 above). Table 1 shows that 1 486 cases (88%) and 1 336 controls (79%) completed the questionnaire, of these 2–3% by telephone interviews. 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 could not contact 42 cases (2%) and 74 controls (4%), mainly since they did not have a telephone or their telephone number was unlisted in the directory.

Table 1

Response rate and causes of non-response among breast cancer cases and controls

	Cases		Controls	
	n	%	n	%
Invited to participate	1 694	(100)	1 705	(100)
Completed questionnaire	1 455	(86)	1 286	(76)
Interviewed	31	(2)	50	(3)
Refused to participate	123	(7)	273	(16)
Too ill to participate	30	(2)	21	(1)
Dead or emigrated before invitation	13	(1)	1	–
Contact not achieved	42	(2)	74	(4)

Between 1 March 1983 and 31 August 1984, 228 BC cases aged less than 40 years at diagnosis were identified. The control group comprised 244 women without BC also aged less than 40 years (dataset 2 above). Of these, 205 cases (90%) and 214 controls (88%) completed the questionnaire.

Potential sources of bias. Since cases and controls were selected from population-based registries, bias arising from the selection process is unlikely. The exclusion of BC patients who died during the one-year lag between diagnosis and data collection, and those who were notified after the completion of the study represented 8% of potential cases. If a strong association was present between the risk of advanced BC and a study factor, the effect of excluding patients with an early death would be an underestimation of the true effect. Although the response rate was fairly high, around 80–90% in this study, the possibility of bias due to non-response cannot be ruled out. A comparison of demographic variables among responders and non-responders (Table 2) showed that within the case and control group, 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. This indicates that the completion of the questionnaire was not influenced by the women's status as a case or a control. Regarding area of residence, there was a significant difference between cases and controls, cases being more likely to live in the capital than controls in the responding and non-responding group. This was expected from the national variation in BC incidence (Fig. 2) and may be interpreted as the present sample being representative of the Danish female population. However, a poorer response rate was obtained for cases living in the capital, while there was no difference in area of residence between responding and non-responding controls.

Efforts were made to reduce recall bias introduced by design and study personnel. The questionnaire was identical for cases and controls and the purpose of the study was stated in general terms, i.e. life-style factors, not revealing specific study hypotheses. The study personnel were not aware of the women's status as a case or a control during data collection and processing. At the time of the study, little public attention was paid to most of the risk factors studied. However, over the past 5–10 years, homeopaths have been using the press to advocate that vitamins and minerals have the potential to cure cancer. As cases filled in the questionnaire one year after the diagnosis, there is a possibility of recall bias in the assessment of vitamins and other dietary supplements. The publication of the study by

Pike et al. in 1983 (35) caused public anxiety about OC and BC risk. When this study was carried out one year later, particularly young BC cases may have been more likely than controls to remember any OC use. Thus, although every measure was taken to reduce bias in this study, the possibility of particular recall bias due to news media attention cannot be ruled out entirely.

Results and comments

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. Marital status at diagnosis was not significantly associated with BC risk (Table 3). There was, however, a significant association with area of residence, women living outside the capital having a lower risk, most pronounced for those living in rural areas. Table 3 shows that the risk estimates were very similar for the women who completed the questionnaire and those invited to the study, indicating that the former were representative of the study population.

Social factors. BC has been associated with high socioeconomic status in both older (20) and more recent (36, 37) correlation studies. The association has been confirmed in many (e.g. 38), but not all (e.g. 39) studies of individuals. Table 4 shows the risk of BC associated with various indicators of social status in this study (40). Compared with women with less than 8 years of education (primary school only), those with 13 or more years of education ran an increased risk. No significant association was found between BC risk and employment status. Elevated risks were seen for women (or their husbands) in white collar jobs and for high social status, but none of the overall associations or the test for trend in social class were significant. In a multivariate analysis including all 5 variables in Table 4 in addition to age, residence and parity, no single social variable was significant when adjusted for the other four, but the contribution from all five just reached significance ($p = 0.04$), indicating an unspecific effect of social status. There may be several explanations why the strength of the reported association between the social status and BC risk has varied between studies. If women of low social status were more likely to be ill and admitted to hospital, then controls chosen from hospital admissions may have been biased towards low social status and the association with BC consequently overestimated. This may have happened in some hospital-based case–control studies (41–44). On the other hand, women who participated in screening programmes (45) may have been biased towards a higher social status, thus underestimating the true association. The measurement of social status has also varied between studies, some using a single indicator, and others indices, combining several social status variables. It is possible that inconsistencies may have arisen

Table 2

Percentage distribution of demographic variables among responders and non-responders

	Responders		Non-responders		Difference between responders and non-responders
	Cases (n = 1 486)	Controls (n = 1 336)	Cases (n = 208)	Controls (n = 369)	
Age at diagnosis					
<40 years	10.0	11.5	8.7	7.0	
40–49 years	28.3	29.1	21.2	24.7	cases: $p = 0.02$
50–59 years	31.2	31.7	29.3	28.7	controls: $p < 0.0001$
60–69 years	30.5	27.7	40.9	39.6	
Difference between cases and controls	$p = 0.31$		$p. = 0.75$		
Marital status					
Unmarried	5.9	4.9	12.0	11.9	
Married	75.8	75.9	61.5	60.4	cases: $p < 0.001$
Divorced	8.6	8.5	12.5	11.7	controls: $p < 0.0001$
Widowed	9.7	10.7	13.9	16.0	
Difference between cases and controls	$p = 0.61$		$p = 0.93$		
Place of residence					
Capital	14.7	9.2	25.0	11.7	
Capital suburbs	15.0	13.0	16.8	13.3	cases: $p = 0.001$
Provincial towns	36.4	40.3	31.7	37.7	controls: $p = 0.51$
Rural areas	33.8	37.5	26.4	37.4	
Difference between cases and controls	$p < 0.0001$		$p < 0.0001$		

Table 3

Risk of breast cancer associated with marital status and area of residence at diagnosis

	Completed questionnaire[1] RR (95% CI)[3]	All invited[2] RR (95% CI)
Marital status		
Married	1.0 (R)[4]	1.0 (R)
Unmarried	1.18 (0.84–1.64)	0.99 (0.75–1.31)
Divorced	1.02 (0.78–1.34)	0.97 (0.77–1.23)
Widowed	0.85 (0.66–1.10)	0.81 (0.64–1.01)
Area of residence		
Capital	1.0 (R)	1.0 (R)
Capital suburbs	0.73 (0.54–0.99)	0.71 (0.55–0.93)
Provincial towns	0.58 (0.45–0.74)	0.55 (0.44–0.69)
Rural areas	0.58 (0.45–0.74)	0.54 (0.43–0.67)

[1] Cases, n = 1 486; Controls, n = 1 336.
[2] Cases, n = 1 694; Controls, n = 1 705.
[3] Age-adjusted relative risk (95% confidence interval)
[4] R denotes reference category

Table 4

Relative risk of breast cancer associated with indicators of social status

Factor	Categories	Number of cases[1]	Number of controls[1]	Adjusted RR (95% CI)[2]	Multivariate RR (95% CI)[3]
Years of education					
	<8 years	587	590	1.0 (R)[4]	1.0 (R)
	8–12 years	546	475	1.08 (0.91–1.29)	1.19 (0.96–1.49)
	13+ years	351	271	1.22 (0.99–1.50)	1.29 (0.96–1.73)
Employment status					
	In work	697	655	1.0 (R)	1.0 (R)
	Unemployed	63	49	1.22 (0.82–1.82)	1.41 (0.90–2.21)
	Stopped working	593	490	1.10 (0.91–1.32)	1.17 (0.95–1.45)
	Never had a job	133	142	0.94 (0.71–1.24)	0.68 (0.44–1.04)
Job type					
	Housewife	253	246	1.0 (R)	1.0 (R)
	Self-employed	54	61	0.84 (0.56–1.28)	0.62 (0.37–1.03)
	White collar	567	445	1.14 (0.90–1.43)	0.76 (0.52–1.10)
	Blue collar, skilled	146	127	1.09 (0.80–1.48)	0.68 (0.45–1.05)
	Blue collar, unskilled	405	400	1.00 (0.79–1.26)	0.71 (0.48–1.04)
Husband's job type					
	Self-employed	336	352	1.0 (R)	1.0 (R)
	White collar	502	406	1.22 (0.99–1.50)	1.31 (1.02–1.69)
	Blue collar, skilled	216	180	1.22 (0.95–1.58)	1.40 (1.00–1.96)
	Blue collar, unskilled	221	230	1.04 (0.81–1.32)	1.34 (0.92–1.94)
Social class					
	5 (low)	272	276	1.0 (R)	1.0 (R)
	4	523	456	1.08 (0.87–1.34)	1.14 (0.76–1.70)
	3	396	375	1.02 (0.81–1.27)	1.13 (0.75–1.71)
	2	156	123	1.21 (0.90–1.62)	1.26 (0.76–2.01)
	1 (high)	84	57	1.35 (0.92–1.98)	1.48 (0.86–2.56)

[1] Women with missing information on any particular factor are excluded.
[2] Relative risk (95% confidence interval) adjusted for age, place of residence and parity.
[3] As 2, but also adjusted for all other factors in the table.
[4] (R) denotes reference category.

from lack of uniformity between measurements. Finally, it cannot be ruled out that indicators of social status are not internationally comparable. In the Nordic countries with populations of similar ethnic and cultural background, free access to medical care, and relatively little difference between rich and poor, the results of the present study, supported by data from Norway (39) and Sweden (38), indicate that the true risk difference between the highest and the lowest social class is in the order of 30%.

Reproductive factors. For more than 100 years, the risk of BC in women has been associated with reproductive factors. The first established determinant was the protective effect of childbearing. In 1970, MacMahon et al. (46) showed in their International Collaborative Study that the protective effect of parity might best be explained by maternal age at first birth from an association between high parity and early age at first birth. Since then, numerous studies have confirmed the association between age at first birth and BC risk. Other reproductive variables, which have been associated with an increased BC risk, include early age at menarche and late age at natural menopause (8). In the present study (Table 5), a significant trend of decreasing BC risk was observed with increasing age at menarche. Dividing the material into four groups according to menopausal status at diagnosis (premenopausal, menopausal, natural and artificial menopause), the trend

Table 5

Risk of breast cancer associated with reproductive characteristics

Factor	Categories	Cases	Controls[1]	RR (95% CI)[2]	p-value for linear trend in RR
Age at menarche					
	<13 years	307	247	1.0 (R)[3]	
	13 years	374	292	1.05 (0.84–1.32)	
	14 years	389	346	0.90 (0.72–1.12)	
	15 years	197	217	0.73 (0.57–0.95)	0.002
	16+ years	161	175	0.75 (0.57–0.98)	
Menopausal status					
	Pre	651	548	1.0 (R)	
	Post	833	786	0.60 (0.47–0.76)	
Age at natural menopause					
	<45 years	56	77	1.0 (R)	
	45 years	185	194	1.30 (0.87–1.96)	0.01
	50 years	297	252	1.60 (1.08–2.38)	
	55+ years	57	41	1.67 (0.98–2.87)	
Termination of 1st pregnancy					
	Full-term (28+ weeks)	1 142	1 116	1.0 (R)	
	Early (−28 weeks)	116	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 years	538	565	0.92 (0.71–1.20)	
	25–29 years	423	358	1.12 (0.85–1.48)	>0.5
	30–34 years	125	114	1.04 (0.74–1.78)	
	35+ years	25	29	0.77 (0.43–1.39)	

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

Table 6

Risk of breast cancer associated with usage

Usage of SH	Premenopausal			Menopausal		
	Cases	Controls	RR (95% CI)[2]	Cases	Controls	RR (95% CI)
Never	517	460	1.0 (R)[3]	68	83	1.0 (R)
Ever	112	78	1.04 (0.74–1.46)	37	36	1.16 (0.64–2.11)
Duration						
<3 years	49	45	0.87 (0.56–1.34)	17	19	1.08 (0.51–2.27)
3 years	26	16	1.15 (0.59–2.23)	8	8	1.10 (0.38–3.21)
6 years	19	4		5	2	
9 years	9	7	1.58 (0.82–3.06)	4	4	1.57 (0.55–4.44)
12+ years	8	4		3	2	
p-value for linear trend in RR			0.29			0.44
Time since first use						
<3 years	20	22	0.73 (0.39–1.37)	9	5	1.84 (0.84–4.04)
3 years	31	19	1.16 (0.63–2.12)	12	8	
6 years	28	11	1.79 (0.87–3.69)	4	11	
9 years	11	13	0.56 (0.24–1.31)	6	7	0.57 (0.25–1.30)
12+ years	19	12	1.15 (0.54–2.43)	4	5	
Time since last use						
<3 years	84	52	1.15 (0.77–1.72)	29	20	1.59 (0.80–3.16)
3 years	10	10	0.73 (0.30–1.79)	6	10	
6 years	4	2	1.00 (0.46–2.17)	1	1	0.53 (0.19–1.45)
9+ years	11	10		–	3	

[1] Women with missing information on any particular variable are excluded.
[2] Relative risk (95% confidence interval), adjusted for age and place of residence.
[3] Reference category for subsequent variables.

in risk was most pronounced in premenopausal women, RR = 0.58 (95% CI 0.36–0.92) for a menarche at age 16 or older compared with a menarche before the age of 13 years (47). This may be due to premenopausal women having a more accurate recall of their age at menarche than postmenopausal women. Alternatively, the protective effect of a late menarche may diminish with advancing age (21). There was a significant trend of increasing BC risk with increasing age at natural menopause (Table 5). When the analysis was restricted to women, who had a natural menopause 5 or more years before the BC diagnosis, menopause at age 55 years or older compared with a menopause before age 45 was associated with a RR = 2.16 (95% CI 1.14–4.09) (47). This was supported by the finding that women still premenopausal at the age of 55 years or more at diagnosis had a more than 2-fold increased risk compared with those who were premenopausal at age 40. Thus, the estimated effect on BC risk of continued menstrual cycles after the age of 50 years was consistent in pre- and postmenopausal women and with the results from other studies (8). No significant association was detected for type of menopause, RR = 1.14 (95% CI 0.89–1.47) for a surgical compared with a natural menopause (48). A bilateral coophorectomy has been suggested to protect against BC (8). However, the self-reported data in the present study were not judged sufficiently reliable to determine the extent of surgery performed. Compared with women whose first pregnancy lasted 28 or more weeks (considered full-term), women whose first pregnancy terminated early, before the 28th week, had an increased BC risk (Table 5). The risk increase was largely confined to women who never completed a subsequent pregnancy, RR = 2.83 (95% CI 1.32–6.07) for a first trimester abortion (induced and spontaneous) (49). Among parous women, no significant association was found between BC risk and abortions, whether these occurred before or after the first full-term pregnancy, during first or second trimester. These findings agree with the results of some (50, 51) but not other studies (52–55). The present study confirmed that full-term pregnancies protect against BC. Never pregnant women had an increased risk and the risk decreased with increasing parity (Table 5). This trend was independent of age at first full-term pregnancy. However, no significant association was detected for age at first full-term pregnancy (Table 5), even after stratification for parity, age at diagnosis, and area of residence (49). Since some other population-based studies from the Nordic countries had either failed to detect an association with age at first childbirth (54, 56) or demonstrated an effect weaker than expected from the literature (57–59), a meta-analysis was conducted to address the influence of age at first birth and

of non-contraceptive sex hormones (SH)[1]

Postmenopausal			Artificial menopause		
Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
325	320	1.0 (R)	87	82	1.0 (R)
166	129	1.28 (0.96–1.71)	116	101	1.04 (0.69–1.57)
29	44	0.89 (0.56–1.41)	30	27	1.01 (0.55–1.85)
23	26	0.93 (0.52–1.68)	16	19	0.81 (0.39–1.70)
30	17	1.82 (0.98–3.37)	17	10	1.52 (0.65–3.53)
23	18	1.34 (0.70–2.54)	23	14	1.44 (0.70–2.96)
47	19	2.32 (1.31–4.12)	28	28	0.88 (0.48–1.64)
		0.002			>0.5
3	4	0.95 (0.45–2.02)	6	7	1.07 (0.53–2.16)
11	12		14	14	
24	23	1.10 (0.60–2.04)	23	14	1.48 (0.71–3.09)
33	33	1.03 (0.62–1.73)	25	19	1.27 (0.64–2.49)
93	50	1.74 (1.19–2.55)	47	45	0.89 (0.52–1.50)
86	60	1.48 (1.01–2.15)	80	67	1.09 (0.70–1.71)
17	16	1.13 (0.56–2.30)	8	12	0.57 (0.21–1.51)
21	21	0.99 (0.52–1.88)	10	3	2.76 (0.73–10.5)
33	26	1.18 (0.68–2.02)	13	14	0.91 (0.39–2.11)

parity on BC risk in the Nordic countries (60). In addition to this study, it included 7 other population-based studies (3 cohort and 4 case-control), the total number of BC cases being 5 568. The meta-analysis confirmed that parity and age at first birth are significant and independent determinants of BC risk. Nulliparity was associated with a 30% increase in risk compared with parous women, and for every 2 births, the risk was reduced by about 16%. There was a significant trend of increasing risk with increasing age at first birth, women giving first birth after the age of 35 years having a 40% increased risk compared to those with a first birth before the age of 20 years. Tests for heterogeneity between studies were not significant for any of the examined variables. Thus, chance sampling error or too insufficient statistical power may have led to the present study failing to detect the association between age at first birth and BC risk.

Exogenous hormones. Oral contraceptives (OC) were released for general use in Denmark in 1966. Currently, one in five women aged 15–49 years use OC (61). Thus, even a weak causal link between OC and BC would have great public health impact. Fig. 6 shows a pronounced age effect in exposure to OC, usage ranging from more than 80% in women aged less than 35 years to less than 10% in women aged 60 years or older. No consistent pattern of higher or lower OC exposure was seen among cases compared with controls. The separate analysis of women aged less than 40 years and those aged 40–59 years (62) generally failed to detect an association between BC risk and characteristics of OC use, such as total duration, duration before and after first childbirth, age at start, time since first use (latency) and time since last use (recency). Results from numerous other studies on the association between OC and BC risk have not been consistent (63). However, when the problem was addressed quantitatively in a meta-analysis (64), a significantly increased risk (RR = 1.46)

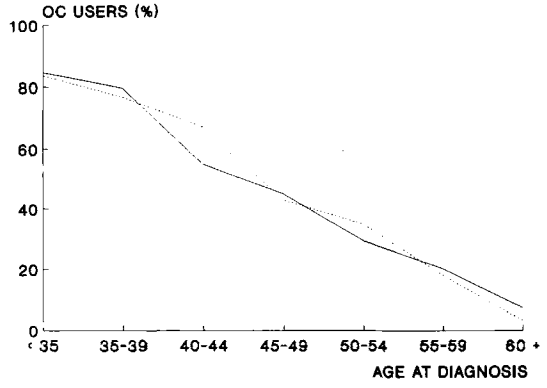

Fig. 6. Ever use of oral contraceptives among breast cancer cases (——) and controls (.....) by age at diagnosis in Denmark (62).

was demonstrated for 10 years of OC use among women aged less than 45 years, or when OC were used for 4 or more years before first full-term pregnancy (RR = 1.72, 95% CI 1.36–2.19). OC were not related to BC in women over the age of 45 years. The present study confirmed that OC were not related to BC in women aged 40–59 years. The lack of an association in women aged less than 40 years is most likely explained by the present material being too small to provide sufficient statistical power to detect an RR in the order of 1.5–1.7. Regarding type of OC, the literature is also inconsistent (65–67). Though non-significant, the results of this study agree with those of the UK National Case-Control Study (67), suggesting that a lower risk was associated with combined OC containing less than 50 μg of oestrogen than with OC containing 50 μg of oestrogen or more. It appears that some of the OC brands marketed before 1975, containing high doses of oestrogen, may be more harmful than modern low-dose pills.

Sex hormones for non-contraceptive purposes were used mainly for the alleviation of menopausal symptoms (47). The overall prevalence of use was 30% in cases and 27% in controls. Table 6 shows that the risk of BC rose with increasing duration of use in all but artificially menopausal women, though the trend was significant only in post-menopausal women. This group was also the only one to show a significant trend ($p = 0.01$) of increasing risk with *increasing time* since first use, i.e. latency. Duration and latency were highly correlated, and it was not possible to determine which of the 2 was the more important. Recency of use was not significantly associated with BC risk. About 3/4 of the women provided information about type of hormones used (Table 7). Exposure to oestrogen or progestagen, alone or in combination, did not affect the BC risk. Sequential therapy with oestrogen and progestagen, whether in one pill or administered in different periods of the cycle or time, was associated with an increased risk, the 2 combined being of borderline significance, RR = 1.36 (95% CI 0.98–1.87). The strongest association, however, appeared for a combination of oestrogen and androgen, RR = 2.31 (95% CI 1.37–3.88). The associations persisted after adjustment for duration of use. In addition to relieving menopausal symptoms, oestrogens seem to reduce the risk of osteoporosis and cardiovascular disease, which are the major causes of morbidity and mortality after the menopause (68). Although oestrogens increase the risk of endometrial cancer, this may be prevented by adding progestagen (69). Thus, the main concern today relates to the association between sex hormones and BC risk. Two recent meta-analyses (70, 71) have found significant heterogeneity between studies in the literature. This may have arisen as a result of the hormone treatments differing or from differences in factors other than exogenous hormones, e.g. type of menopause. Despite these inconsistencies, it is likely that the BC risk increases with increasing duration of use in excess of 5 years. After 15 years of oestrogen use, the RR may range from 1.3 to 2.5 (71). The risk may also increase with increasing dose of oestrogen (70). The influence on BC risk of adding a progestagen to the oestrogen treatment has been addressed only in one other study (72), which reported a 4-fold increased risk associated with such combined therapy for more than 6 years. These results agree well with those of the present study, suggesting that the addition of a progestagen may be more harmful than oestrogen treatment alone. However, more studies with data of high quality are needed to confirm this hypothesis.

Table 7

Risk of breast cancer in relation to types of sex hormones used

	Cases (%)[1]	Controls (%)	RR (95% CI)[2]
None	997	945	1.0 (R)[3]
Oestrogen (E)	171 (35.1)	167 (42.9)	0.97 (0.76–1.25)
Progestogen (P)	14 (2.9)	12 (3.1)	1.02 (0.46–2.22)
E + P, combination	8 (1.6)	13 (3.3)	0.63 (0.26–1.53)
E + P, sequential	62 (12.7)	41 (10.5)	1.41 (0.93–2.13)
E + P, other	49 (10.1)	30 (7.7)	1.33 (0.83–2.14)
E + Androgen	56 (11.5)	21 (5.4)	2.31 (1.37–3.88)
E + P + Androgen	16 (3.3)	11 (2.8)	1.26 (0.58–2.74)
Unknown	111 (22.8)	94 (24.2)	1.09 (0.82–1.47)

[1] Percentage of users; cases n = 487, controls n = 389.
[2] Relative risk (95% confidence interval) adjusted for age at diagnosis, place or residence, and menopausal status
[3] Reference category.

Anthropometry. The association between BC risk and anthropometric variables is complex. Several large cohort studies have found that a high BMI decreased the risk of premenopausal BC and increased the risk of post-menopausal BC (73–77). In some (73, 76, 78), but not all cohort studies (74, 75), the risk of BC increased with increasing height in all age groups. The present study failed to demonstrate any association between BC and anthropometric variables (height, current weight, BMI, weight 10 and 20 years before diagnosis, and at age 20 years) in pre- and postmenopausal women (47). Among women being menopausal or with an artificial menopause, weak trends were observed toward increasing risk with increasing height and current weight, but these disappeared when both factors were considered simultaneously in the BMI. In the present study, anthropometric variables were self-reported. Although self-reported figures correlate strongly with the actual measurements, it has been shown that tall and heavy women tend to underestimate their height and weight, while small and thin women produce overestimates (79–81). It is thus possible that the present lack of association was due to systematic misclassification.

Dietary factors. Over the past 5 years, many reports have reviewed evidence that diet is involved in BC aetiology (82, 83). Fat is the macronutrient which has been evaluated most thoroughly. Across populations there

Table 8

Relative risk of breast cancer associated with total fat intake

Fat intake in quartiles[1]	Cases n	Controls n	RR (95% CI)[2]
1 (low)	332	358	1.0 (R)[3]
2	356	335	1.17 (0.95–1.45)
3	381	309	1.37 (1.11–1.70)
4 (high)	388	302	1.45 (1.17–1.80)
p-value for linear trend in RR			<0.001

[1] This covers about 80% of total fat intake which in Danish women ranges from 35 to 184 g per day with a median of 95 g per day (87).
[2] Relative risk (95% confidence interval) adjusted for age at diagnosis and place of residence.
[3] Reference category.

appears to be a strong positive correlation between dietary fat intake and BC but it may not be causal. In studies at the individual level within populations, i.e. cohort and case–control studies, the association has been much weaker or absent. Table 8 shows that we found a highly significant trend of increasing BC risk with increasing total fat intake, RR = 1.45 (95% CI 1.17–1.80) for the highest quartile compared with the lowest (30). The estimates were not influenced by further adjustment for social and reproductive risk factors; in particular, the effect of fat intake did not differ between pre- and postmenopausal women. As mentioned earlier, it was not possible to evaluate the potentially confounding effect of total energy intake, since the questionnaire was not designed to estimate energy intake. The importance of this variable became evident only after the completion of the study (31). Combining data from the American nurses' cohort (84) and an international correlation study (85), Goodwin & Boyd (86) estimated that the maximum RR to be detected in a population like the American (with 32–44% of calories from fat) would be about 1.4. This estimate is very close to what we found for Danish females, whose energy percentage from fat ranged from 21 to 63 with a mean of 42 (87). Our results agree with those of a recent Canadian cohort study (88), but are at variance with two American cohort studies (84, 89), which failed to detect any association with intake of total fat, RR = 0.82 for the highest quintile of intake compared with the lowest among the American nurses (84). The various components of fat intake has been addressed by others, but could not be evaluated in the present data. A combined analysis of 12 case–control studies of diet and BC (90) showed a significantly increased risk (RR = 1.46) associated with a high intake of saturated fat in postmenopausal women. Data from other case–control studies (91–93) support this, whereas the cohort studies (84, 89) found no association with saturated fat. The most recent evidence points toward a decreased BC risk associated with a high intake of poly-unsaturated fatty acids, demonstrated in premenopausal Singapore Chinese women (94), postmenopausal Moscow women (93) and Australian women (92). Compared with fat, other constituents of diet have received relatively little attention. Our study was designed specially to evaluate intakes of β-carotene, tea, coffee, and sweeteners. The reported consumption of vegetables as well as the estimated intake of β-carotene from vegetables was not related to BC risk (30). Other studies (90, 93, 94) have observed decreased risks associated with a high intake of β-carotene, though analyses of plasma or serum β-carotene have produced equivocal results (95–97). It is possible that the present lack of association may be due to misclassification, since 95% of the study subjects overestimated their intake of specific vegetables when compared with an overall frequency of vegetable consumption. Another Danish study (98) has confirmed that it is difficult to obtain a valid estimate of vegetable consumption. In connection with the suggested protective effect of β-carotene and of vitamin C (90, 93), the association between standard multi-vitamin tablets and BC risk was also of interest. Such vitamin supplements are taken by a fairly large proportion of Danish women, about 70% in this study. Contrary to expectation the RRs were elevated, though not significantly. However, as mentioned earlier an influence of recall bias cannot be ruled out. The role of consumption of tea, coffee and other methylxanthine-containing substances in relation to BC is not clear (99, 100). This study showed no association between BC risk and consumption of tea and coffee and is therefore in agreement with the majority of other studies. Usage of sugar or artificial sweeteners in tea and coffee were also not related to BC risk. Summarizing the evidence on diet and BC risk, it is apparent that inconsistencies exist which cannot merely be ascribed to chance. For fat intake for instance, the results of the largest American cohort study reported (84) are at variance with those from the combined case–control analysis (90). To help resolve this difference it is important that future studies focus on studying the entire diet, foods and nutrients (calories, macro- and micronutrients), not concentrating on single components which was the general trend before the mid 1980's. Over the past 5 years, interesting results have emerged suggesting protective effects of diet, e.g. β-carotene and vitamin C. Since diet is a complex mixture, where the consumption of one component seems to affect the consumption of others, it is possible that the relation to BC may be determined by some favourable or unfavourable balance between animal and plant products. Another possibility is that diet during adolescence may have a greater influence on BC risk than adult diet (101).

Alcohol. Prior to 1982, little attention was paid to the association between alcohol consumption and BC risk. Since then, the issue has been addressed in more than 30 studies. Longnecker et al. (102) performed a meta-analysis of data available up to 1988 and demonstrated a dose–response relation to increasing BC risk with increasing alcohol consumption. Relative to abstaining, a daily of

consumption of 24 g of ethanol (or about 2 drinks) was associated with RRs in the order of 1.4–1.7. Results of some later studies (93, 102–106) agree with these estimates. Other studies (107–109) have not been able to demonstrate a dose–response relation, and their findings are not inconsistent with the estimates produced by Longnecker et al. (102). However, in one cohort (110) and 3 case–control studies (111–113) no association was found between alcohol consumption and BC risk, these studies thus being at variance with the above. Practically all studies agree that any risk increase was not confined to particular types of alcoholic beverages, suggesting an effect of alcohol per se. Our data supported this (114). However, we detected a complex interaction between alcohol consumption and age at diagnosis and dietary fat intake, i.e., the association of alcohol consumption with BC risk differed by age group and fat intake. Age-stratified analyses showed no significant association between alcohol consumption and BC risk in women aged less than 50 and 60 years or more at diagnosis. Among women aged 50–59 years, however, there was a significant interaction between alcohol and fat intake. Fig. 7 illustrates that the BC risk increased with increasing alcohol consumption among women in the lowest quartile of fat intake, the RR being almost 18-fold higher for consumers of 24 g of alcohol or more per day compared with abstainers. In women with a higher fat intake, there was no clear association between alcohol consumption and BC risk. The present results agree with those of Richardson et al. (103), who also found that the association with alcohol was most pronounced in women with a low fat intake. In other studies, an increased risk was not influenced by adjustment for dietary factors (104, 105, 115–119). Results similar to ours were reported by Adami et al. (111), who noted a slightly decreasing risk with increasing alcohol consumption in women aged less than 45 years. However, in most other studies the association with alcohol did not vary with age.

We were not able to identify sources of bias which could explain the interaction between alcohol, age, and fat intake, but it cannot be ruled out that it occurred due to chance. Testing the alcohol-fat interaction in each of the 3 age groups, the possibility of it being significant ($p < 0.05$) in at least one group, by chance, is 14%. Despite the large number of investigations demonstrating a positive association between alcohol consumption and BC risk, the question of causality still remains. The association appears weak (RR < 2) and the range of alcohol doses to yield this association has varied considerably, from less than 1 to 60 g per day. Such heterogeneity makes an interpretation difficult. Furthermore, the measurement of alcohol consumption has been rather crude, most examining only current consumption, and probably subject to measurement error. Finally, the carcinogenic action of alcohol is not fully understood (120) and no biological mechanism has been established to explain how alcohol should affect breast carcinogenesis. Future studies should focus on characterising alcohol consumption in the same way as other carcinogenic exposures, i.e. by establishing ages at start and end of exposure, duration, latency and recency.

Smoking. It has been proposed that smoking may reduce the risk of BC, possibly due to an 'anti-oestrogenic' effect (121). Few studies have supported this, but the majority of studies have failed to show any association between smoking and BC risk (122). A few other studies have found an increased risk. Meara et al. (107) suggested that the contrasting results might be attributed to bias in the selection of cases and controls. They and others (123, 124) have concluded that reliable results on the association between smoking and BC are likely to come only from population-based studies. Among women in the present study, the proportion who had ever smoked was very similar for cases and controls, 66.0% and 66.5% respectively (122). Current smokers and ex-smokers had a similar risk of BC to non-smokers, the RR estimates being 0.93 (95% CI 0.78–1.10) and 0.98 (95% CI 0.80–1.24). No dose–response relation was observed for any measure of smoking (age at start, duration, number of cigarettes per day, or cigarette-years of exposure) in all subjects, and when pre- and

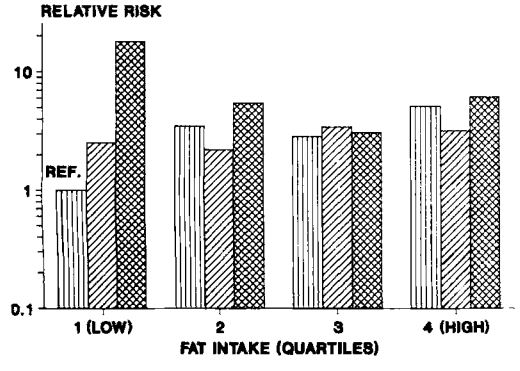

Fig. 7. Combined effect of dietary fat intake and alcohol consumption in grams per day $_0$ $_{1-23}$ $_{24+}$ on breast cancer risk in women aged 50–59 years in Denmark.

Table 9

Breast cancer risk in relation to age at commencement of smoking among heavy smokers

	Cases n	Controls n	RR (95% CI)*
Never smoked	503	446	1.0 (reference)
Smoked 20 or more cigarettes per day	120	132	0.76 (0.57–1.02)
Age started (years)			
<15	16	16	0.87 (0.42–1.77)
15–19	68	69	0.84 (0.58–1.21)
20–24	19	28	0.56 (0.30–1.02)
25+	17	19	0.70 (0.36–1.38)

* Relative risk (95% confidence interval) adjusted for age at diagnosis and place of residence

postmenopausal women were examined separately. A recent study (125) reported increased risks (RR = 1.5–2.4) associated with young age at commencement among women smoking 25 or more cigarettes per day. In this study (Table 9), women smoking 20 or more cigarettes per day had a non-significantly decreased risk and the association with age at commencement was not significant (126). Thus, the present population-based study supports that smoking is not associated with the risk of BC.

Biological mechanisms

The present study has contributed to the evidence that female sex hormones are involved in the aetiology of BC by confirming risk factors related to endogenous hormones, such as early menarche, late natural menopause, and nulliparity, and by demonstrating an increased risk associated with long-term usage of non-contraceptive sex hormones in postmenopausal women.

Over the years, a number of theories have been proposed to explain the underlying biological mechanism, whereby sex hormones, in particular oestrogen and progesterone, may be involved. In 1969, Cole & MacMahon (127) suggested that a woman's lifetime risk of BC is inversely related to the amount of oestriol (E3) relative to the amount of oestrone (E1) and oestradiol (E2) (E3/(E1 + E2)) that she produces during the decade or more following menarche. Later, Korenman (128) stated the 'oestrogen window hypothesis', the basic concept being that the breast tissue is most susceptible to tumour induction in periods when oestrogen stimulation is unopposed by progesterone ('open' oestrogen window) and less susceptible at other times ('closed' oestrogen window). The risk is determined by the duration of 'open oestrogen windows'. Siiteri (129) directed the attention to the role of sex hormone binding globulin (SHGB). The serum level of SHBG correlates inversely with the level of free E2 in serum and may therefore influence the availability of oestrogen to the target tissues. Recently, Key & Pike (130) have pointed out that our knowledge about the hormonal control of breast cell division is incomplete and that two hormonal explanations should be considered. As one explanation, they suggest the 'oestrogen plus progestagen hypothesis', according to which an increased exposure to oestrogen alone will cause some increase in BC risk but the risk will be increased much more by exposure to oestrogen and progestagen together. The alternative explanation, the 'oestrogen alone hypothesis', is that oestrogen alone determines the BC risk and that progestagens are irrelevant.

All hypotheses are more or less consistent with the risk factors demonstrated in epidemiological studies. However, measurements of sex hormones (E1, E2, E3, total oestrogen, % free E2, SHBG, pregnanediol, progesterone, and testosterone) in urine or blood have produced inconsistent results (130). Thus, none of the hormonal hypotheses have been completely refuted or proved. There is a clear need for more studies to address the hormonal control of breast cell division, under normal conditions, during treatment with sex hormones and during the carcinogenic process.

Conclusion

This case–control study, based on the entire Danish population, has demonstrated associations between BC risk and demographic, hormonal and dietary factors. Table 10 summarizes these risk factors and the magnitude of the risk estimates.

The general problem with BC risk factors is the strength of the associations, the majority beng rather weak with RRs not exceeding 2. At this level, the possibility of confounding by some yet unrecognized factors cannot be ruled out. So far, no single exogenous factor has been identified, causally related to BC, to which the majority of cases could be attributed, as for instance tobacco smoking and lung cancer. Thus, with regard to primary prevention, this study as many others has failed to suggest sensible measures which could reduce a woman's risk of developing BC.

Future prospects of primary prevention depend on an understanding of BC aetiology. Current evidence, supported by this study, indicates that many factors act together to determine the risk of BC. Some of these factors may reflect a common underlying biological mechanism, possibly related to a particular hormonal profile. Although none of several hormonal hypotheses has been proved, the present findings on hormonal replacement therapy support the 'oestrogen plus progestagen hypothesis'.

In order to gain control over BC as an important health problem, the search for clues to BC aetiology should continue, in particular to establish the role of diet and the complex relationship between diet and hormonal profile. Meanwhile, it is necesary to focus on secondary prevention (early diagnosis through screening) and tertiary prevention (improved BC treatment) in order to reduce morbidity and mortality from BC.

Table 10

Risk factors for breast cancer. Summary of the Danish case–control study

Factor	High risk	Low risk	Magnitude of risk estimate
Residence	Urban	Rural	2
Socio-economic status	High	Low	1.3
Age at menarche	Early	Late	1.3
Age at natural menopause	Late	Early	1.7
Parity	Low	High	2
Hormonal replacement therapy	5+ years of use	None	2
Dietary fat intake	High	Low	1.5

Characteristics of survival after breast cancer

Material and methods

Among the 2 705 BC patients, diagnosed from 1 March 1983 to 31 August 1984, 260 were excluded from the analysis of survival (123 due to death before data collection, 14 due to notification after study collection, 40 due to a previous BC and 83 because of an in situ cancer) (131). Of the remaining 2 445 patients, 2 137 (87%) completed the questionnaire on risk factors. For 1 744 of these, complete information was available from the BDCG on 6 clinical and pathological characteristics of the BC (size of the primary tumour, invasion of skin and fascia, grade, number of lymph nodes removed during surgery, and number of positive lymph nodes, i.e. with metastatic spread). The information from DBCG was incomplete for 213 patients, mainly because they were not enrolled in treatment protocols, and absent for 180 because these were identified solely from the cancer registry, which only records extent of disease as localized, regional spread, and distant metastases. We compared the survival of patients with (n = 1 744) and without (n = 393) complete BDCG information and found no significant difference.

By computerized record linkage to the CPR all patients were followed up to record their vital status by 30 June 1990 (end of follow-up), using personal identification numbers. Survival was calculated from the date of diagnosis to the date of death, emigration or end of follow-up, the latter two being treated as censored observations in the analysis.

Relationships between study variables and survival were investigated using the Cox proportional hazards method (132), to carry out two-tailed tests of statistical significance and to obtain hazard rates and 95% CI. RR estimates were computed using the statistical software package EGRET (34).

Results and comments

Fig. 8 shows the survival of 2 568 patients aged less than 70 years with a primary invasive breast cancer, the 5-year survival rate being 72%. Of the 2 445 patients surviving the first year after diagnosis and thus entering the study, 805 (33%) had died, 3 had emigrated and 1 637 (67%) were still alive by 30 June 1990.

In relation to demographic variables (Table 11), the risk of dying was not significantly associated with marital status or age at diagnosis. Compared with patients living in the capital, those living in the suburbs had a significantly lower risk of dying. This may be explained by the latter having smaller tumours and fewer positive lymph nodes than the former. Women who did not complete the questionnaire had an almost 2-fold increased risk of dying, probably reflecting that non-responders more often had advanced disease.

In a multivariate analysis of the clinical and pathological variables (Table 12), 4 turned out significant, tumour size, skin invasion, number of positive lymph nodes, and grade.

Table 11

Relative risk of dying according to demographic characteristics among 2 445 breast cancer patients, diagnosed in Denmark, 1983–1984

Characteristic	Levels	Number of deaths/patients	Adjusted RR (95% CI)[1]
Age at diagnosis, years			
	<50	272/883	1.0 (R)[2]
	50+	533/1 562	1.12 (0.96–1.30)
Residence at diagnosis			
	Capital	145/381	1.0 (R)
	Suburbs	101/361	0.70 (0.54–0.91)
	Other	559/1 703	0.86 (0.71–1.04)
Marital status			
	Single	224/660	1.0 (R)
	Married	581/1 785	1.00 (0.86–1.18)
Completed questionnaire			
	Yes	658/2 137	1.0 (R)
	No	147/308	1.93 (1.61–2.31)

[1] Relative risk (95% confidence interval) adjusted for the other characteristics listed.
[2] R denotes reference category.

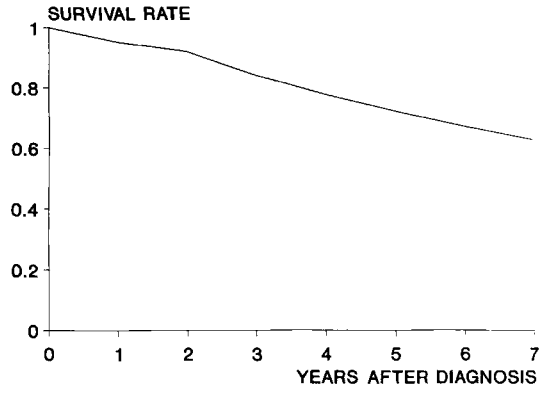

Fig. 8. Survival of 2 568 breast cancer patients diagnosed in Denmark, 1983–1984 (131).

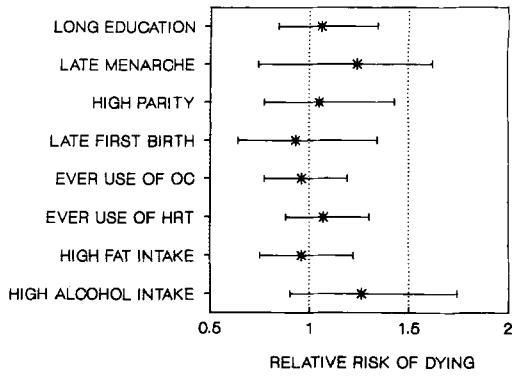

Fig. 9. Relative risk of dying (with 95% confidence intervals) in relation to factors, which affect the risk of developing breast cancer (OC = oral contraceptives, HRT = hormonal replacement therapy).

Risk factors for developing BC, i.e. incidence risk factors, were examined in a model including these 4 significant clinical variables, age and residence (Fig. 9). There was no significant association between survival and social status (evaluated by years of education), reproductive variables (age at menarche, menopausal status, time between diagnosis and menopause, number of pregnancies, age at first birth, time since last pregnancy), usage of oral contraceptives, hormonal replacement therapy and dietary variables.

This lack of association is in agreement with results from some studies (133–135). However, others (136, 137) have demonstrated a better survival in women of high than of low social class and the influence of parity seems to vary with the age of the patients (138–140). Thus, the literature has not provided consistent results.

In contrast, the literature is quite consistent with regard to body weight or BMI, overweight or obese women being reported to have a poorer prognosis than lean women. In some studies (134, 135, 141, 142) this relation persisted for all stages of disease, while others (143–146) have found that the lower survival associated with obesity was restricted to patients with early stage disease.

When we defined early disease as tumours of 3 cm or less, no skin invasion, no positive lymph nodes and grade I (n = 424) and all others as advanced disease (Fig. 10),

Table 12

Relative risk of dying according to clinical characteristics among 1 744 breast cancer patients, diagnosed in Denmark, 1983–1984

Characteristic	Levels	Number of deaths/patients	Adjusted RR (95% CI)[1]
Tumour size, mm			
	0–30	359/1 366	1.0 (R)[2]
	31–50	110/279	1.22 (0.98–1.53)
	51+	64/99	1.88 (1.39–2.54)
Skin invasion			
	No	477/1 649	1.0 (R)
	Yes	56/95	1.49 (1.09–2.02)
Number of positive lymph nodes			
	None	212/1 021	1.0 (R)
	1–3	172/500	1.76 (1.43–2.16)
	4+	149/223	3.88 (3.09–4.88)
Grade			
	I	167/782	1.0 (R)
	II	268/738	1.75 (1.44–2.12)
	III	98/224	2.38 (1.85–3.07)

[1] Relative risk (95% confidence interval) adjusted for the other characteristics listed and for age; stratified for residence.
[2] R denotes reference category.

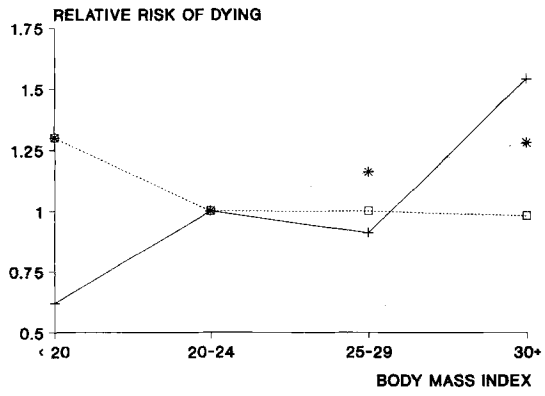

Fig. 10. Relative risk of dying by body mass index (kg/m^2) among breast cancer patients with early disease (-+-+-), advanced disease unadjusted (-*-*-) and adjusted (-□-□-) for other clinical variables, as defined in text.

our results on early disease agree well with those of Tretli et al. (146), who reported RR = 1.70 (95% CI 1.29–2.25) for the 5th quintile of relative BMI. The RR-estimates in Fig. 10 did not reach statistical significance, which may be due to the present series being much smaller than that of Tretli et al. (146) including a total of 8 427 patients.

In patients with advanced disease, an apparently poorer survival among obese women was explained in part by a higher frequency of positive lymph nodes. By adjusting for the clinical variables, the RR-estimate for a BMI of 30 or more decreased from 1.28 to 0.98. Fig. 10 also shows an increased risk of dying associated with a BMI less than 20 (RR = 1.38, 95% CI 0.97–1.73) and that the estimate remained unchanged by adjustment for the clinical variables. This is in accordance with other data (146, 147) suggesting that the shape of the hazard function for the association between BMI and risk of death from advanced disease was quadratic rather than linear, i.e. that low as well as high BMI was associated with an unfavourable prognosis. Irrespective of body weight, a weight loss of 5 kg or more indicared a poor prognosis in this study. It is possible that low BMI and weight loss may be further measures of disease progression representing part of the residual variance in stage not measured by other variables.

The lack of an association between height and breast cancer survival is consistent with other studies (124, 135, 145, 146).

Conclusion

The present study supports that survival after BC may be associated with body mass in a complex fashion related to stage of disease. Apart from the anthropometric variables, our results do not confirm that factors, which are associated with an increased risk of developing BC, influence the survival. It is possible that the incidence risk factors operate in the early, preclinical stage of the carcinogenic process, but loose their importance once the tumour has reached a certain size or metastatic potential.

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