The association between mammographic patterns and previous use of oral contraceptives among premenopausal women at age 25-35 in Northern Norway

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Abstract:

High risk mammographic patterns represent an increased risk of developing breast cancer and may be used as a surrogate endpoint for the disease. We examined the relationship between previous use of oral contraceptives and present mammographic patterns classified in a modified Wolfe classification system. The data was collected from the first 52 participants in the EBBA (**E**nergy **B**alance **B**reast Cancer **A**spects) study. The participants in the EBBA study were closely followed through a whole menstrual cycle and a number of different variables were collected. Mammograms were obtained in the first part of the menstrual cycle. Information about previous use of oral contraceptives was obtained through a questionnaire.

The mammographic patterns were divided into 4 catagories with catagory 1 having the lowest density and 4 having the highest density. Further all mammograms were classified with the letter a or the letter b. Letter a meaning that there is fibroadenomatosis present in the breast and letter b meaning there fibroadenomatosis is not present.

Odds Ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression and adjusted for age, age at menarche, height, BMI and parity. The group who had never used OC was defined as the reference group with OR = 1.

We tested the association between breast density and total years of OC use. Since n was low (n= 49) we found it necessary to divide the catogories of years of total OC use by the median, this was the only way to get a minimum of participants in each cell/ group. We performed three sets of tests. In the first set we divided the breast density into two catogories; Density 1+2 and Density 3+4. OR for a higher breast density in the group with less than 4.5 years of OC use was 0.35 (95% CI: 0.035- 3.522) and OR in the group that had used OC in more than 4,5 years was 0.49 (95 % CI 0.054- 4.496). In the second set we dived the breast density into three catagories: density 1+2, density 3 and density 4. OR in the group with less than 4.5 years of OC use was 0.47 (95% CI was 0.1- 2.27) and OR in the group with more than 4.5 years of OC use was 0.48 (95% CI was 0.1- 2.29). In the third set of analysis we tested the possible association between fibroadenomatosis pattern (two catagories; present or not present) and total years of OC use. In the group of women that had used OC for more than 4.5 years the OR for having a fibroadenomatosis pattern on their mammogram was 4.51 (95% CI was 0.71- 28.8). We did not find any significant associations between OC use and neither mammographic density or fibroadenomatosis pattern. This is not in accordance with previous studies on the same subject.

Introduction:

Breast cancer is the most frequently diagnosed cancer worldwide, and ranks number one as a cause of cancer death among women 35 to 54 years of age in the western world. Breast cancer is also the most common cancer among Norwegian women in terms of mortality and morbidity, and must be considered as a public health problem. The incidence of the disease in Norway have been increasing since 1953 (see figure 1) and in 1998 more than 2300 breast cancer cases were diagnosed . Each year close to 800 women die of this disease, among whom 50% are under the age of 70 (1)

To study potential risk factors related to this common type of cancer is therefore in general of great interest. Moreover, high risk mammographic patterns represent an increased risk of developing breast cancer and may be used as a surrogate end point for the disease in research concerning the aetiology and prevention of breast cancer (2)

When hormonal contraceptives were introduced in the 1960s in general, women achieved an improved way to control their reproductive lives. This form of contraceptives soon became popular in Norway and the sale has been steadily increasing since 1967 (see figure 3 and table 1,2)

Oral contraceptives can be divided into two main groups; the progestin only pill and the combined progesterone and estrogen pill (which again can be subdivided into the monophasic and the triphasic preparations). In addition there are hormonal contraceptives that are not orally administrated; the gestagen releasing intrauterine device, gestagen depot injection, subcutan gestagen implantate and a vaginal device (Nuva- Ring) releasing low doses of estrogen and gestagens. Combined OCs and progestin- only pills prevent pregnancy through different mechanisms: Combined OCs inhibit ovulation and down regulate the production of hormones by the ovaries by a negative feed back effect on the pituitary gland. Whereas the progestin- only pills act mainly by increasing the viscosity in the cervical mucus making this a less penetrable barriere for the sperm cells.

The relationship between oral contraceptives (OCs) use and the risk of breast cancer has been controversial for several decades. Recent studies (3,4) have however shown that current/recent use of OCs is associated with an increased risk of breast cancer. The effect is highest among current users and vanishes within 10 years after cessation of use (3). Use of combined OCs and progestin-only pills seem to increase the risk at the same level (4).

The aim of the present study is to examine the relationship between previous OC use and the different breast patterns (modified Wolfe classification)(5) observed in our population- participants

in the EBBA study- 52 women age 25-35 from Northern Norway. We asked if previous use of oral contraceptive may have had an influence upon present mammographic patterns.

Background

The incidence of breast cancer increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically (see figure 2).
Age adjusted incidence and mortality varies by up to a factor of five between countries (6).
Developmental factors such as low age at menarche and high age at menopause are associated with an increased breast cancer risk. These risk factors are both strongly correlated to the number of ovulatory cycles and thus act by increasing the total life exposure to estrogen and progesterone.
Age at menarche and menopause, parity, and lactation all influence a woman's lifetime exposure to oestrogen (7).
The association between oral contraceptives (OCs) use and the risk of breast cancer have been analysed in several studies, and in particular use of combined OCs has been reported to slightly increase breast cancer risk. Among the fewer amount of studies that have reported on the relationship between OC use and mammographic patterns or densities, one study found a positive association between OC use and high risk patterns(8).
As suggested by Pike and Spicer the increased risk of breast cancer due to OC use found in some studies is explained by the oestrogen and progestin hypothesis; i.e. when the total amount of exogenous hormones exceeds that of a normal menstrual cycle an increased risk may be experienced (9). In addition such therapy increases breast density in many women and can lead to impaired sensitivity of mammographic screening.
Hormone replacement therapy is known to increase the risk of breast cancer. In the WHI- study 16000 postmenopausal women where randomised for treatment with either a combination of estrogen and progestin or placebo. The study was stopped after five years because of increased incidence of breast cancer in the hormone therapy group. In extended analyses of data from this study it was found that not only was the incidence of breast cancer increased in the hormone group, but the cancers in this group were of a more aggressive character (10).
Etiologic studies of breast carcinoma have indicated that weight, body mass index (BMI), and breast tissue density are important determinants of a woman's risk for the disease. Obesity is associated with a twofold increase in the risk in postmenopausal women whereas among premenopausal women it is assosiated with a reduced incidence. (11). Increases in serum

bioavailable oestrogen are thought to be one of the likely mechanisms for the increased breast cancer risk associated with obesity at postmenopausal age.
Two breast cancer genes, BRCA1 and BRCA2, have been identified and account for a substantial proportion of very high risk families. Both genes are very large and mutations can occur at almost any position (6), but this known mutation cannot explain all familial aggregation(2)
(See table 1)

Breast density and mammographic patterns:

The distribution between glandular tissue, fibrous connective tissue (stroma) and fat determines the mammographic density of a breast tissue. Radiographically glandular tissue and fibrous connective tissue have similar x- ray properties. Together they are referred to as fibroglandular or "mammographic density". Fat is less attenuating than fibroglandular tissue and thus appears darker in a mammographic image.

One has observed an association between breast density and risk for breast carcinoma. Women whose mammograms show a high breast density have an increased risk for developing breast carcinoma compared to women whose breast parenchyma consists primarily of fat and therefore has a low mammographic density (12). High risk mammographic patterns represent and increased risk of developing breast cancer and may be used as a surrogate end point for the disease in research concerning the aetiology and prevention of breast cancer (8)
It is not exactly known why a high breast density increases the risk for breast cancer. The "simple" explanation may be that in a dense breast the number of glandular cells are higher and this increases the absolute risk for one of the cells to undergo malignant transformation (2).
Furthermore; high breast density makes it more difficult to evaluate a mammogram. Therefore, women with high breast density are at double risk because in addition to that the risk of developing the disease is increased, it is less likely that a tumour in a dense breast will be detected in an early stage (2).

Hormones and mammographic patterns:

Epidemiological studies have repeatedly shown that hormonal factors make an influence upon breast density and mammographic patterns (8).

The endogenous hormones oestrogen and progesterone, which are secreted during the menstrual cycle stimulate the proliferation of epithelial cells in the breast (13).

Known risk factors for breast cancer, such as early menarche, parity and age at first birth, have been found to be independently associated with high risk mammographic patterns (8).

As previously mentioned is the risk associated with oral contraceptives controversial. However, if there is a risk, it is likely that it works through increased of hormone levels.

Many different studies have shown that postmenopausal hormone replacement therapy, in particular oestrogen and progestin replacement therapy, also increases breast density and are associated with high risk mammographic pattern (8).

Histopathological aspects of breast cancer:

Histologically the female breast is composed of a glandular epithelium (supported by a basement membrane), connective- and adipose tissue. The glandular tissue is arranged in 15- 20 lobes. Each breast lobe is again divided into smaller units; terminal ductal lobules (14).

Cancer may develop in different tissues in the breast and histological classification criteria are established by the WHO (Histological Typing of Breast Tumours. WHO 1981.Geneva, Switzerland)

The majority of breast cancers are carcinomas, subdivided into lobular and ductal carcinomas. Even though it is now believed that all invasive carcinomas have their origin in terminal duct lobular units, this is a morphological classification that still is valid. Ductal carcinomas constitute 70-80 % and lobular 5-10% of all malignant breast cancers. (15)

Material and Methods

Subjects

The women in our study participated in the EBBA (Energy Balance Breast cancer Aspects) study who took part in 2001- 2002. The aim of the EBBA study is to analyse the association between lifestyle and biomarkers of breast cancer risk among women in Norway and Poland. The EBBA data base represent the first data material with measured free biological fraction of oestradiol and progesterone through a whole menstrual cycle on pre- menopausal women in Norway.
A total of 402 women, aged 25-35 from 2 geographical areas (city and rural) represented by 206 women from Norway and 196 women from Poland were included in this study.
The women were asked to participate in the study through posters in the local environment and adds in local newspapers. Individuals was screened by interview for adherence to the following criteria: Regular menstruation (normal cycle length 22 – 36 days for at least 6 cycles), no use of steroid contraceptives within the last year, no pregnancy or lactation in the past year, no history of gynaecological disorders, weight: within 20 % of ideal body weight standards for height and no chronic disorders. These criteria were set to reduce the impact of confounding variables known to be associated with altered ovarian function.

All participants filled out a general questionnaire. The questionnaire was brought to the first visit, here a trained nurse checked it for inconsistencies.

The questionnaire collected the following information:

- General information: Place of birth, ethnicity, number of siblings, educational level and working activity.
- Information about height and weight: Height and weight at birth, at age 18 and at present.
- Subjective thoughts upon body size compared to people at the woman's own age (at age 3-7, age 7- 12 and age 13- 16).
- Information about menstruation, parity and breast feeding: Age of menarche, time between menarche and regular menstrual cycles, if menstruation cycles have been regular or not and

cycle length. Number of childbirths, time of childbirths and time of breast feeding for each child. Drug treatment for nausea during pregnancy.

- Physical activity: By filling in various tables participants were asked to evaluate degree of physical activity in different areas as house keeping, sport activities, activity level at work/ education, transport to/from work/ education institution. Activity level in the different areas were to be evaluated both during the last year and during life.
- Medication history
- Cancer history in the family
- Lifestyle: Smoking habits, alcohol habits.

History of OC use

All women were asked to fill in an questionnaire about previous use of different types of hormonal contraception including oral contraceptives (progestin only pill, monophasic combination pill and triphasic combination pill), IUD and contraceptive gestagen injection Depo- Provera. Information about age at start, length of use and type of contraceptive was collected.

Dietary record

Caloric, protein, fat and carbohydrate intake was estimated for each participant. The subjects recorded the total dietary consume during two periods, 7 days in total. All weekdays were represented. The first period started after the first day of the cycle and continued for the 4 following days. The second period started at the beginning of the third week of the cycle, and the remaining 3 weekdays were now recorded.

The women were instructed to eat and drink as normal, and the importance of recording everything they ate and drunk during these days was emphasized.

Physical activity:

The daily log was to be recorded every day during the cycle. Each participant did register hours of sleep, time of saliva sampling, bleeding or not, and types and duration of different activities every day. Here by including; transport, activity level at work, house keeping and spare time activities.

Each kind of activity had its own code that was registrated in the form and was graded with a intensity between 1 and 4, with 4 being the highest.

Clinical parameters and laboratory methods:

The participants were followed through one menstrual cycle by the same trained nurses at the clinical research department at the University Hospital in Northern Norway (UNN). The women themselves collected daily saliva samples for hormone analysis using RIA (radioimmunoassay technique).
During this period the women had 3 visits/ clinical examinations at the university clinic; the first visit at the 1st cycle day, the second visit at the 12th cycle day and the third visit at the 21st cycle day.

At the first visit the following data were obtained:

- Weight
- Height
- Hip/waist ratio
- Skinfold thickness on upper arm and back
- Blood pressure
- Hart rate
- Bloodsamples for analysis of: Hemoglobin, leukocytes, CRP, blood glucose, calcium, albumin, creatinin, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, serum oestrogen, serum progesterone, serum LH, serum FSH, serum testosterone, SHBG, DHEASO4

At the second visit and third visit following data were obtained:

- Skinfold thickness at upper arm and back
- Blood pressure
- Pulse
- Bloodsamples for analysis of: leucocytes, CRP, serum oestrogen, serum progesterone, serum LH, serum FSH, SHBG.

Mammographic patterns:

Mammograms obtained in the first part of the menstrual cycle were classified in a modified Wolfe classification system.(5) This system divides the mammograms from 1- 4, with 1 having the lowest density and 4 having the highest. Further, fibroadenomatosis was classified with the letter a and no fibroadenomatosis with the letter b (see table 4).

Dexa Scan (Dual x-ray absorptiometry)

Dexa scan were taken of the participants in the first part of the menstrual cycle.
The total body assessment using DEXA provides a unique capability of non-invasive measurement of skeletal bone status, as well as lean and fat tissue components including percent fat, lean tissue mass etc.

Statistical analysis:

All data were punched into a Microsoft Access data base, control read by trained personnel and made available for statistical analyses. Multiple logistic regression analyses were performed using the logistic procedure in the SAS and SPSS statistical packages. In addition Microsoft Excel was used for graphical design.
We performed three different sets of analysis. In all three sets the population was adjusted for age, age at menarche, height, BMI and parity and a 95% confidence interval was used.
The group with never users of OC was defined as reference group with Odds Ratio(OR) = 1.
We tested the association between breast density and total years of OC use. Since n was low (n= 49) we found it necessary to divide the categories of years of total OC use by the median, this was the only way to get a minimum of participants in each cell/ group.
In the first set divided the breast density into two categories; Density 1+2 and Density 3+4. In the second set we dived the breast density into three categories: density 1+2, density 3 and density 4.
In the third set of analysis we tested the possible association between fibroadenomatosis pattern (two categories; present or not present) and total years of OC use.

Results:

General characteristics:

The mean age of the women in our population were 30 years (min. 25, max 35). The mean age of menarche was13,5 years and the average menstrual cycle length was 28 days.
15 of 52 participants (28,8 %) had been giving birth to one or several children, and the mean age at first birth was 27,2 years. The average number of children in the population was 0,4.
The mean BMI was 24,1 (min 19,4 max 33,9) and the average height was 167 cm (min 151, max 182)

17 (34 %) of the participants (n=50) had fibroadenomatosis patterns on theirs breast mammograms. In the fibroadenomatosis group (n =17) one woman was classified with breast density 1 (5,9 %), no one with breast density 2, nine women with breast density 3 (52,3 %) and seven women with breast density 4 (41,2 %).
In the group with no fibroadenomatosis present on their mammograms (n = 33) was no one classified with breast density 1, twelve women were classified with breast density 2 (36,4 %), fourteen women with breast density 3 (42,4 %) and seven women with breast density 4 (21,2%).
High risk patterns are in this modified Wolfe classification defined as 3a and 4a. In our total population (n =50) 16 women (32 %) had this high risk pattern represented on their mammograms.

75,5 % of the population (n = 49) had used oral contraceptives.
The pattern of use of oral contraceptives in the population is illustrated with different variables in table 6. Here we see that the mean age at start of OC is 19.3 years and that the mean of total use is 4,5 years. The average age at stop of using OC is 25 years and the mean time since stop of using OC is 5.4 years.
Further we see that the sequence pill has been more commonly used than the monophasic pill; the mean for total years of use of the sequence pill is 2.3 compared to 1.9 for the monophasic pill (n = 37). The progestin- only pill however has not been frequently used; only two women out of a population of 49 have been using the progestin- only pill and the mean for the duration of use is 1.8 years.

Risk by Breast Density of OC Use

In the first set of test we divided the breast density into two catogories; 1+2 and 3+4.
Women having ever used OCs appeared in this test to present a lower risk of having a dense mammogram. OR for a higher breast density in the group with less than 4.5 years of OC use was 0.35 (95% CI: 0.035- 3.522) and OR in the group that had used OC in more than 4,5 years was 0.49 (95 % CI 0.054- 4.496). (Test for trend p = 0.61;Table 7)
We note here that the confidence intervals are extremely large and therefore no conclusion may be drawn from this test.

In the second set we dived the breast density into three catagories: density 1+2, density 3 and density 4. Neither in this set of analyses did we find a positive association between breast density and total years of OC use OR in the group with less than 4.5 years of OC use was 0.47 (95% CI : 0.1- 2.27) and OR in the group with more than 4.5 years of OC use was 0.48 (95% CI 0.1- 2.29). (Test for trend p = 0.4; Table 8)

Risk by fibroadenomatosis by OC use.

In this third set of analysis we tested for a possible association between fibroadenomatosis pattern and total years of OC use. In the group of women that had used OC for more than 4.5 years the OR for having a fibroadenomatosis pattern on their mammogram was 4.51 (95% CI ; 0.71- 28.8) (Test for trend: p= 0.07; Table 9)

Discussion

34% of the women in our study had fibroadenomatosis patterns on theirs breast mammograms, and further 42.4 % of these women had breast density 3 and 21.2 % had breast density 4. We consider these numbers rather high. One may ask if selection bias can explain this result; many of the women in the study had a positive family history of breast cancer and one may ask if many of them are under a higher basal risk compared to the common population and that the high percentage of high risk pattern found in the study is an expression for this assumed higher risk.

In our study we could not find any significant associations between OC use and neither breast density or fibroadenomatosis. This was not expected since previous studies done on the same types of variables where one has found a positive association between breast density and OC use (8).

It is in this context important to point at the fact that in our study n was low (n = 49). Data on mammography and OC use was not available for all 200 participants in EBBA for our study. This fact had several implications; one is that we had to divide the catogories of total years of OC use with the median (4.5 years). A higher number of participants may have done it possible to design other types of catogories that have been more in accordance to standard literature on this subject.

Further several types of bias should be discussed. First recall- bias may have been of significant importance in our study. The questionnaire asked detailed questions about OC use for a long period of time. One should also note that the participants filled out the form after the main study was completed and one must assume that the concentration and motivation to answer accurately was not as good at this point as it was during the active participation in the study. In addition the fact that not using oral contraceptives for the past year was a criteria for inclusion in the EBBA study may have resulted in a population that to a lesser extent have been using oral contraceptive than the average mean. We consider the mean for time since stop of using OC (5.4 years) as rather high and will expect this to have been lower if other inclusion criteria had been used.

A strength of the EBBA study in general is that n is high (n = 200) and that a large number of information about the participants were collected. This gives the possibility to correlate for a much higher number of variables than we have done in our little study.

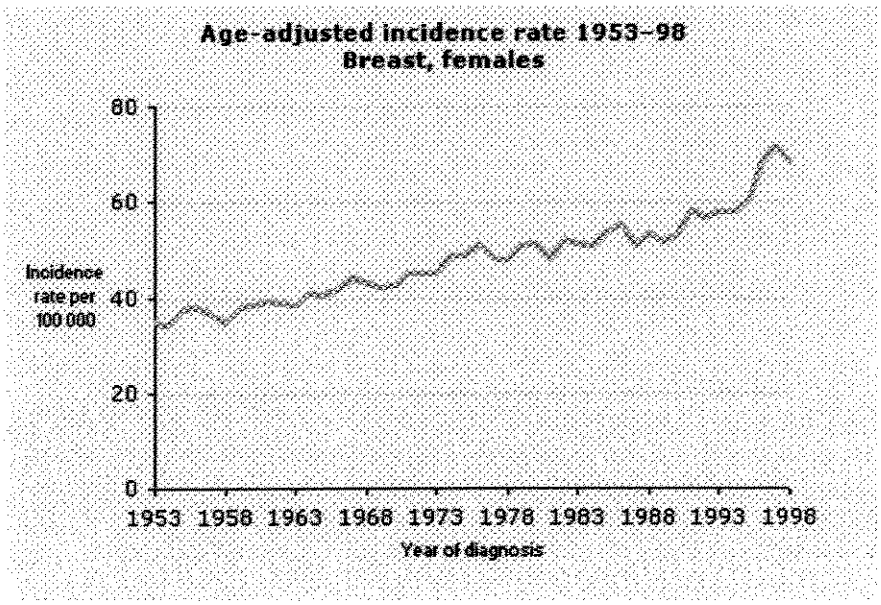
Conclusion

In conclusion no significant association between mammographic patterns and previous OC use were found. Since this is not in accordance with previous studies on the same types of data one may assume that our results would have been different if data from all participants in the EBBA study had been used, this would have given a n = 200.
Therefore we suggest that in the future the same types of analyses should be done, but this time on the whole EBBA population.

Acknowledgements

Participants in the EBBA study. Inger Thune. Anne- Sofie Furberg, Peter Ellison, Nils Bjurstam. The Norwegian Cancer Society, The Norwegian Research Council, Aakre Foundation, Klinisk Forskningspost University hospital Northern Norway, Sanitetsforeningen

Figure 1: The incidence of breast cancer in Norway. Numbers from the Norwegian cancer registry 1998.



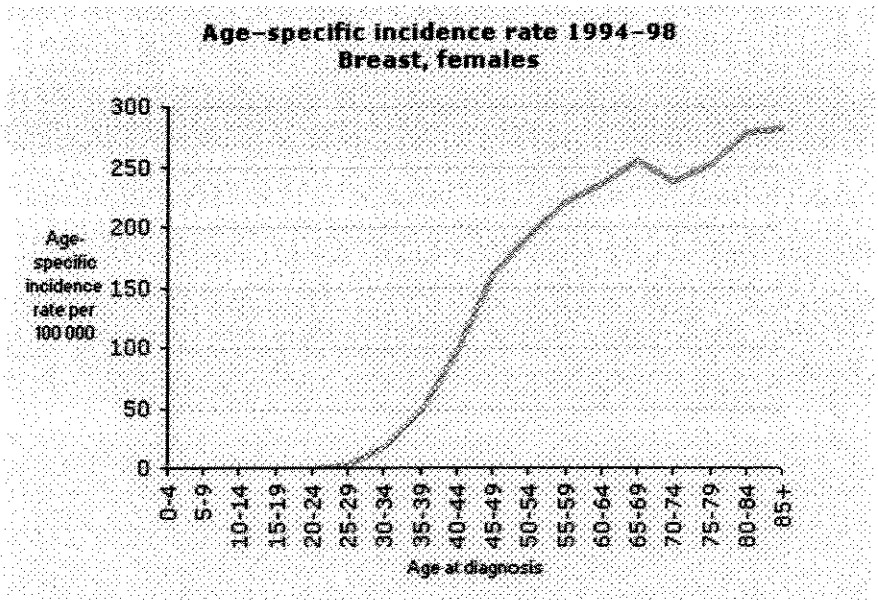
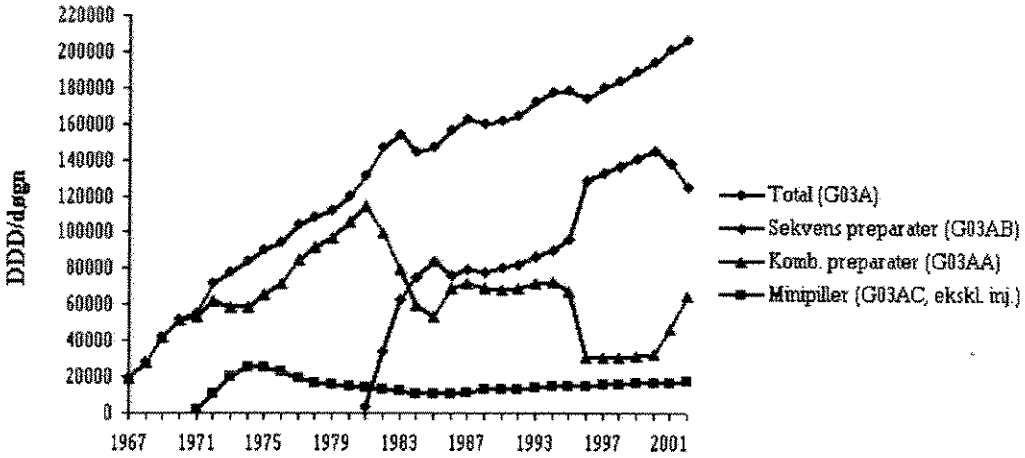


Figure 2: Age- specific incidence rate of breast cancer in Norway. Numbers from the Norwegian cancer registry 1998.

Figure 3: Sales of Hormonal Contraceptives for systemic use in Norway. 1967 – 2002. Numbers from Legemiddelverket 2002.



Figur 4: Mammographic patterns: Density 1- 4. Fibroadenomatosis: a: present, b: not present.

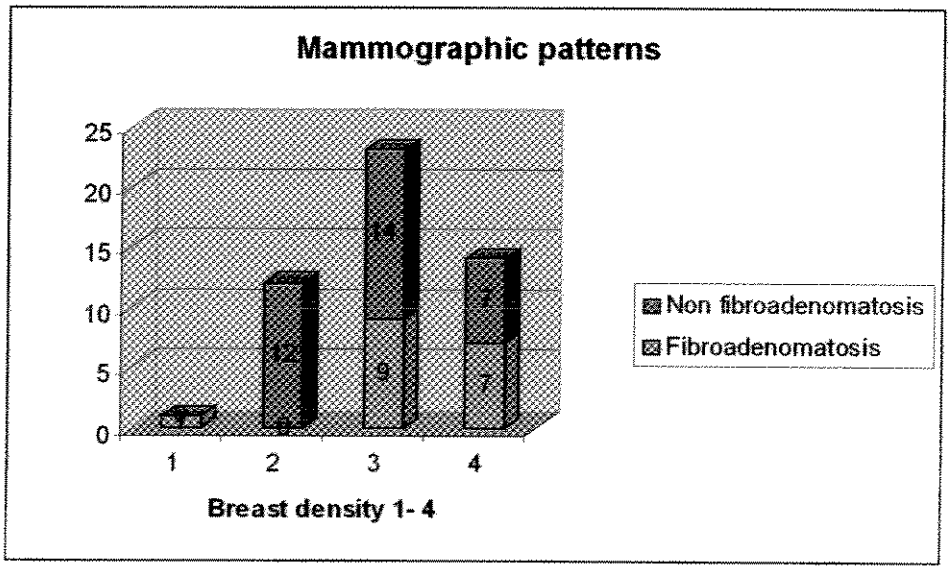


Table 1: Established and probable risk factors for breast cancer. From Mc Pherson K, Steel CM, Dixon JM. Breast cancer- epidemiology, risk factors and genetics. BMJ 2000

Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	2 ≥	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmenopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age 10
Taking exogenous hormones:		
Oral contraceptives	1.24	Current use
Hormone replacement therapy	1.35	Use for ≥ 10 years
Diethylstilbestrol	2	Use during pregnancy

Table 2: Sales of systemic hormonal contraceptives in Norway 1998- 2002. Sales given in DDDs/day, which gives an estimate of number of users. Numbers from Legemiddelverket 2002

	Year	1998	1999	2000	2001	2002
G03A A	Progestogener og østrogener, faste kombinasjoner	30800	31500	32100	45900	64300
G03A B	Progestogener og østrogener, sekvensprep.	135700	141300	145100	137900	124420
G03A C	Progestogener (orale)	16000	16570	16810	16900	16630
G03A C	Progestogener (inj)	7000	8980	12270	16130	19460
G03A C	Progestogener (implantat)					270
	Total	189500	198350	206280	216830	224810

Table 3: Sales of local hormonal contraceptives in Norway 1998- 2002

	Year	1998	1999	2000	2001	2002
G02B A03	Plastspiraler med progestogener	16700	20900	23400	25660	27670
G02B B01	Vaginal ring med progestogen og østrogen (reg. okt. 2002)					5430

Table 4: EBBA Mammograph classification system

Fibroadenomatosis (Y/N)	Density 1	Density 2	Density 3	Density 4
A (fibroadenomatosis)				
B (No fibroadenomatosis)				

Table 5 . Base- line characteristics of the study population in the EBBA study.

General characteristics:	n =52	Mean	Range	Std. Deviation
Age (years)		30,0	25,1- 36,6	2,82
Body Mass Index: (kg/ m2)		24,1	19,4- 33,9	3,59
Height (cm)		166,8	151,0- 182,0	7,30
Weight (kg)		67,2	46,6- 98,6	11,4
Age at menarche (years)		13,5	11,4- 17,0	1,33
Cycle length (days)		28,4	22,0- 36,0	2,39
Length of time until periods became regular (years)		1,73	1,00- 4,00	1,09
Parity:				
Ever had children (y/n)			1,00- 2,00	0,46
Age at first birth(years)		27,2	20,0- 32,4	3,30
Number of children		0,44	0,00- 3,00	0,78
Breast feeding:				
1st child (months)	n=15	-	2,6- 10,3	6,30
2nd child (months)	n=7	11,0	13,1-19,0	2,85
3rd child (months)	n=1	9,0		

* Number of women may vary due to missing information

Table 6: Characteristics of OC use

	N= 37	Mean	Median	Range	Std. Deviation
Age at start of 1. period of use of OC		19.3	19.0	15.0- 27,0	3.1
Age at stop of last period of use of OC		25.0	24.5	18.0- 29.0	3.0
Time since stop of last period of use of OC		5.4	4.9	1.1- 12,3	3.0
Monophasic pill, total years		1.9	1.5	0-11,0	2.6
Sequence pill, total years		2.3	0.5	0- 10.0	3.0
Mini-pill, total years		0.1	-	0- 2,5	0.4
Depo-provera, total years		-	-	-	-
IUD, total years		-	-	-	-
Other contraceptive, total years		-	-	-	-
Unknown contraceptive, total years		0.2	-	0.3- 7.0	1.2
Sum contraceptives, total years		4.5	4.5		3.2
Users of monophasic pill (total years)	23	3,1	2,0	0,1-11,0	2,6
Users of sequence pill (total years)	23	3,7	3,3	0,2- 10,0	3,0
Users of progestin- only pill (total years)	2	1,8	1,8	1,0- 2,5	1,1

Table 7: Odds Ratio for having increased Breast Density according to duration of OC use

	Breast-Density 1-2 (cases)	Breast-Density 3-4 (cases)	OR* (Odds Ratio)	95% CI (Confidence Intervall)
Never users	3	9	1.00	
< 4.5 years	5	13	0.35	(0.035- 3.522)
> 4.5 years	5	14	0.49	(0.054- 4.496)
P for trend			0.61	

* OR adjusted for age, age at menarche, height, BMI and parity

Table 8: Odds Ratio for having increased Breast Density according to duration of OC use.

	Breast Density 1-2(cases)	Breast Density 3(cases)	Breast Density 4(cases)	OR* (Odds Ratio)	95% CI (Confidence interval)
Never users	3	5	4	1.00	
< 4.5 years	5	7	6	0.47	(0.1- 2.27)
> 4.5 years	5	11	3	0.48	(0.1- 2.29)
P for trend				0,4	

* OR adjusted for age, age at menarche, height, BMI and parity

Table 9: Odds Ratio for having Fibroadenomatosis according to duration of OC use.

	Fibro-Adenomatosis (cases)	No Fibro-adenomatosis (cases)	OR* (Odds Ratio)	95% CI (Confidence interval)
Never	3	9	1.00	
< 4.5 years	3	15	0.66	0.09- 5.04
> 4.5 years	10	9	4.51	0.71-28.8
P for trend			0.07	

* OR adjusted for age, age at menarche, height, BMI and parity

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