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Oral contraceptives and benign breast disease

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According to Smallwood and Taylor [1], 'benign breast disease is an umbrella term given to a wide spectrum of common non-malignant disorders of the female breast'. We can say that benign breast disease includes the histological disorders of the breast, excluding invasive cancer. Recently, Hughes et al. [2] proposed the acronym ANDI or 'aberrations of normal development and involution' to cover a number of benign conditions in the breast that confer no cancer risk and which are individually common and which can be related to phases of reproductive life.

Assessment of risk for later carcinoma development is of impelling interest to physicians who treat benign breast disease. Dupont and Page [3] refer to two different groups according to histological characteristics: non-proliferative disease and proliferative disease. Table I shows the classification of benign breast disease according to the relative risk for invasive breast carcinoma based on histological examination of breast tissue without carcinoma.

Epidemiology of benign breast disease

Benign breast disease is the most common type of breast disease and is important because the condition commonly recurs, produces discomfort and may be confused with breast cancer. Among benign breast diseases, cystic disease of the breast may occur in up to 50% of premenopausal women. Table II reports data about the occurrence and incidence of non-proliferative disease of the breast [3].

Cystic disease of the breast is a term which has been used to describe a variety of conditions in which palpable breast cysts are the dominant feature. Palpable breast cysts may be accompanied by a host of microscopic lesions, including microcysts, apocrine change, adenosis, fibrosis and epithelial hyperplasia [4]. Cysts occur most frequently during the period of breast involution, in women aged 40–50 years, and least frequently in the period after the menopause.

Fibroadenoma is a common lesion that develops from lobules during pubertal growth or sometimes in response to lactation. Although histologically divisible into the pericanalicular type and the intracanalicular type, the two types may coexist. Most of these lesions become clinically apparent between the ages of 15 and 25. Many women, however, have silent fibroadenomas which, because of their deep location within dense breast tissue, are clinically undetected [5].

Epidemiology of oral contraceptive use

Combined oestrogen–progestagen

oral contraceptives (OCs) have been used for more than 30 years, and in 1988 it was estimated that, worldwide, more than 63 million married women used OCs [6]. Such widespread use must be justified by a favourable risk/benefit ratio. Published data show that OCs have a protective effect against ovarian and endometrial cancers [7 8], although there is controversy regarding the effects of OCs on the breast.

In the past, OCs contained much higher dosages of oestrogen and progestogen than at present. These changes in the composition of OCs in the first 10 to 15 years of their use have complicated the evaluation of their role in breast disease. It is unclear if the risk of breast disease from the current low-dose OCs differs from that of the high-dose preparations studied earlier.

Table I: Benign breast disease according to the relative risk for invasive breast carcinoma

1. No increased risk — non-proliferative disease
   - 1.1 Mild epithelial hyperplasia of usual type
   - 1.2 Microcysts and macrocysts (cystic disease of the breast)
   - 1.3 Duct ectasia
   - 1.4 Fibroadenoma
   - 1.5 Apocrine metaplasia
   - 1.6 Adenosis, sclerosing or florid

2. Slightly increased risk (1.5–2 times) — epithelial proliferative disease without atypia
   - 2.1 Hyperplasia of usual type, moderate or florid

3. Moderately increased risk (4–5 times) — atypical hyperplasia
   - 3.1 Atypical ductal hyperplasia
   - 3.2 Atypical lobular hyperplasia

4. High risk (8–10 times) — carcinoma *in situ*
   - 4.1 Lobular carcinoma *in situ*
   - 4.2 Non-comedo ductal carcinoma *in situ*

Table II: Epidemiology of non-proliferative disease of the breast

Mild epithelial hyperplasia of usual type	19.0%
Microcysts	32.1%
Macrocysts (> 1 cm)	22.9%
Epithelial calcifications	11.4%
Fibroadenomas	11.5%
Apocrine metaplasia	27.8%

Relationship of oral contraceptives to risk of benign breast disease

Table III shows the data of different case–control studies concerning the relationship between OCs and all types of benign breast disease [9]. The protective effect of OCs was evident in all studies, except in the study by Nomura [10], in which the control group can be criticized. More recently, Odenheimer et al. [17] conducted a study in 90 pairs of twins where one of the twins had biopsy-confirmed or clinically diagnosed benign breast disease. A protective effect of OCs was recognizable in both groups.

The duration of OC use and the composition of OCs with regard to the progestogen dose must be considered. With regard to the duration of use, most studies show a significant difference between the women who have at one time or another used OCs and the long-term users who have used OCs for a minimum of 2 years. The long-term use of OCs for more than 8 years was associated with a pronounced protective effect compared with the non-use of OCs [18]. Corresponding data are also available with respect to the correlation between the duration of OC use and the rate of hospitalized treatment. According to studies by

Table III: Case-control studies of the relationship between oral contraceptives and the risk of benign breast disease (all types)

Reference	No. cases	Relative risk		Minimum years of use by long-term users
		ever-users	long-term users	
[10]	320	1.14	—	—
[11]	255	0.60	0.47	6
[12]	98	0.47	—	—
[13]	1048	0.99	0.69	5
[14]	446	0.80	0.20	8
[15]	366	0.81	0.35	5
[16]	419	0.72	0.48	2

Table IV: Case–control studies of the relationship between oral contraceptives and the risk of fibroadenomas

Reference	No. cases	Relative risk		Minimum years of use by long-term users
		ever-users	long-term users	
[11]	86	0.43	—	—
[13]	71	1.20	1.74	2
[15]	123	0.92	0.10	5
[16]	106	1.06	0.58	2
[20]	—	0.35	—	—
[21]	251	0.57	—	—

Vessey et al. [11], OC use of 2 years or more leads to a reduction in hospitalizations by about 75%.

With regard to the dose of progestogen, the studies conducted by the Royal College of General Practitioners [19] provide evidence that the protective effect of OCs increases with the dose. For three doses of norethisterone acetate, the rates of incidence of benign breast disease were 7.18 for 1 mg, 4.27 for 3 mg, and 3.57 for 4 mg.

Relationship between oral contraceptives and risk of fibroadenomas

Table IV shows the data of different case-control studies concerning the relationship between OCs and fibroadenomas (9 20 21]. The influence of OCs on the development of fibroadenomas is less evident. The duration of OC usage, the age of the woman, and the presence of intracanalicular epithelial proliferation can modify the protective effect of OCs.

Canny et al. [21] found a negative correlation between OC use and fibroadenoma formation for women younger than 45 years. In contrast, there was no protective effect of OCs in women aged 45 years and older. However, Ramcharan et al. [22] observed only a slightly reduced risk of fibroadenoma in 18- to 19-year-old women after more than 2 years of OC use.

Vessey et al. [11] came to the conclusion that the use of OCs leads to a reduction of hospitalised treatments for fibroadenomas and that the duration of use plays a substantial role in this. The lowest rate was found in the group with a duration of use of more than 2 years.

Relationship between oral contraceptives and risk of cystic disease

Table V shows data from different case-control studies concerning the relationship between OCs and cystic disease [9]. The duration of OC usage, the progestogen component, and the degree of epithelial atypia can modify the protective effect of OCs.

The studies of Sartwell et al. [13], Kelsey et al. [15] and Ravnihar et al. [16] reported a marked protective effect against cystic disease in women who had used OCs for a long time. Brinton et al. [20] described that OCs with the highest dose of progestogen were correlated with the lowest risk of cystic disease.

The results of different studies dealing with the morphology of cystic disease in relation to OC use are inconsistent. Hsieh et al. [23] observed a distinct protective effect of OCs against the development of cystic disease irrespective of the degree of epithelial atypia. This result contrasts with those of two other studies [24 25] which found a distinct protective effect of OCs only in respect to cystic disease with mild to moderate or no epithelial atypia. There was no significant difference between OC users and non-OC users as regards cystic disease with severe cellular atypia.

Table V: Case–control studies of the relationship between oral contraceptives and the risk of cystic disease

Reference	No. cases	Relative risk		Minimum years of use by long-term users
		ever-users	long-term users	
[11]	117	0.67	—	—
[13]	306	0.85	0.49	2
[15]	211	0.83	0.30	5
[16]	266	0.66	0.45	2

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