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Papers

Breast Cancer Risk and History of Selected Medical Conditions Linked with Female Hormones

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The relation between history of several medical conditions and procedures and risk of breast cancer was evaluated in data from a hospital-based case-control study of 2663 cases of breast cancer and 2344 controls with acute conditions unrelated to any of the established or potential risk factors for breast cancer. Whereas previous diagnosis of diabetes mellitus, thyroid disease, hypertension at any age, hyperlipidaemia, cholelithiasis, pelvic inflammatory disease and physician-diagnosed subfertility were unrelated to cancer risk, history of severe obesity in postmenopausal women (odds ratio [OR] 1.4), benign breast disease (OR 1.8) and history of breast biopsies (OR 2.4) were associated with significant risk elevation. Conversely, lifelong history of menstrual irregularities (OR 0.6) seemed to confer some protection against onset of breast cancer. This study supports the hypothesis that, unlike endometrial cancer, breast cancer risk is not enhanced by medical conditions known or suspected to be linked with female hormones, with the exception of benign breast disease and severe overweight in postmenopausal women.
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INTRODUCTION

SEVERAL hormones and growth and inhibitory factors are known or suspected to influence the development of normal and neoplastic mammary tissue. There is evidence that breast cancer risk is enhanced by increased exposure to oestradiol [1]. It seems, however, that the free oestradiol concentration (i.e. that not bound by sex hormone binding globulin [SHBG]), rather than the total is critical [2]. Oestrogens alone have little proliferative potential for breast epithelium, but progesterone or some of the products of the anterior pituitary (e.g. prolactin) may play an important synergistic role. Glucocorticoids, insulin, and triiodothyronine (the most active thyroid hormone) have also been suspected to be important cofactors in the proliferation and differentiation of mammary tissue [1]. Conversely, prolactin inhibitory factor and α-fetoprotein are thought to control or block the growth of mammary tumours [3].

Many such factors are altered in some medical conditions (e.g. diabetes, hypertension and diseases of the thyroid, liver, and gallbladder) [2, 3]. These are chronic conditions that show substantial variations in their prevalence according to age and gender as well as to variables such as parity, age at first birth and menopause, which are recognized risk factors for breast cancer [1, 4].

Diseases of the thyroid [5] and gallbladder [6] are in excess in women. Non-insulin dependent diabetes mellitus is strongly associated with obesity in both genders but, in societies where men are leaner than women, it is also more prevalent in women

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than men [7]. Parous women are more likely than nulliparous women to die from diabetes, gallbladder diseases and several circulatory disorders, including hypertension, while nulliparity is associated with increased mortality from uterine leiomyoma [4]. Interestingly, an increased risk of hypertension and, perhaps, gallbladder diseases and diabetes have been found in oral contraceptive (OC) users [8] who, in turn, are protected against ovarian cysts [9], uterine leiomyomas [10] and, possibly, benign breast disease [11]. Finally the menopause is accompanied by striking changes in the prevalence of such conditions [7].

Some chronic conditions may influence breast cancer risk [12–14] as has been shown for endometrial cancer [2], either overall or in some subgroups of patients (e.g. women who were diagnosed with hypertension before last pregnancy [3] and postmenopausal obese women [1]).

To establish whether any such conditions, in addition to some diseases of the female genital tract and breast, are significantly associated with breast cancer risk, we took advantage of a case-control study in which the participants had been asked about any history of several medical conditions potentially related to female hormones.

SUBJECTS AND METHODS

Since January, 1983, we have been doing a case-control study of breast cancer in the greater Milan area [15]. Trained interviewers identified and questioned women admitted to university and general hospitals in the area for breast cancer and for a wide range of other conditions. Overall participation rate was 98% for cases and 97% for controls.

The cases were women below the age of 75 with histologically confirmed breast cancer diagnosed within the year before interview, and who had been admitted to the National Cancer Institute and to the Ospedale Maggiore (which includes the four largest teaching and general hospitals in Milan). 2663 cases, aged 26–74 (median 54) were interviewed.

Patients who were admitted for acute conditions to several specialized university clinics and to the Ospedale Maggiore of Milan were eligible as controls. The catchment areas for cases and controls were similar (overall, 87% of cases and 90% of controls resided in the same region, Lombardy). Controls had diseases that were not malignant, hormonal, or gynaecological, diagnosed within the year before interview. 2344 controls, aged 25–74 (median 55) were interviewed. Of these, 32% were admitted for trauma (mostly fractures and sprains), 27% had non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 17% were admitted for acute surgical conditions (mostly abdominal), and 24% had other illnesses. Although cases and controls were not matched for age, their characteristics by 5 year age group were similar (Table 1).

A standard questionnaire was used to obtain information on sociodemographic factors, general characteristics and life-style; frequency of use of selected dietary items and beverages; reproductive and menstrual factors; and history of thirteen medical conditions or procedures, selected on the basis of their known or suspected relation with female hormones.

The odds ratios (ORs) for breast cancer, with the 95% approximate confidence interval (CI) and, for multiple levels of exposure, linear trend tests were computed from data stratified for decade of age [16]. To allow simultaneously for the effects of several potential confounding factors, multiple logistic regression with maximum likelihood fitting was used [15]. Since cases and controls were different in education, age at first birth and menopausal status, terms for such factors, in addition to age, body mass index (kg/m^2) and history of the disease under examination, were included in the regression equations.

Table 1. Distribution of 2663 cases of breast cancer and 2344 controls

	Breast cancer cases (%)	Controls (%)
Age (yr)		
< 35	103 (3.8)	169 (7.2)
35–44	534 (20.1)	411 (17.5)
45–54	791 (29.7)	654 (27.9)
55–64	711 (26.7)	650 (27.7)
≥ 65	524 (19.7)	460 (19.6)
Education (yr)*		
≤ 6	1391 (52.2)	1411 (60.2)
7–11	743 (27.9)	564 (24.1)
≥ 12	529 (19.9)	369 (15.8)
Parity		
0	493 (18.5)	475 (20.3)
1–2	1607 (60.3)	1278 (54.5)
≥ 3	563 (21.1)	591 (25.2)
Age at first birth (yr)†		
< 25	878 (40.5)	915 (49.1)
25–29	830 (38.3)	644 (34.6)
30–34	356 (16.4)	216 (11.6)
≥ 35	106 (4.9)	88 (4.7)
Menopausal status*		
Pre	1123 (42.2)	880 (37.6)
Post	1540 (57.8)	1464 (62.5)

*χ^2_1 (trend) ≥ 3.84, $P < 0.05$.
†Figures do not add up to total because of a few missing values.

RESULTS

Among all cases and controls, a history of diabetes mellitus, thyroid disease, hypertension, hyperlipidaemia, uterine leiomyoma, pelvic inflammatory disease and physician-diagnosed subfertility were unrelated to breast cancer risk (Table 2). A small, non-significant increase of risk was noted in those women who had had cholelithiasis (OR 1.2) whereas some reduction, of borderline statistical significance, was seen with a history of ovarian cysts or benign tumours (OR 0.8). A history of severe obesity (i.e. body mass index 28 kg/m^2 or higher) was associated with a 1.3 fold increased risk (95% CI 1.1–1.5), while the most elevated OR emerged for history of benign breast disease (OR 1.8, 95% CI 1.5–2.2) and breast biopsies (OR 2.4, 95% CI 1.6–3.6). Conversely, menstrual irregularities (i.e. lifelong frequency of menstrual-like episodes of bleeding less than 21 or more than 35 days apart) conferred significant protection against onset of breast cancer (OR 0.6, 95% CI 0.5–0.7). When major breast cancer determinants in the present data set were allowed for, no substantial change in OR was observed.

In Table 3 the effect of the same selected medical conditions on breast cancer risk is examined in strata according to menopausal status and parity. Although no association was observed in most

Table 2. Relation between history of selected diseases and breast cancer risk

Diagnosis	No. (%) with diagnosis		OR (95% CI)	
	Breast cancer cases	Controls	MH*	MLR†
Diabetes	125 (4.7)	113 (4.8)	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Thyroid disease	230 (8.6)	180 (7.7)	1.1 (0.9–1.4)	1.1 (0.9–1.4)
Severe overweight	363 (13.6)	263 (11.2)	1.3 (1.1–1.5)	1.3 (1.1–1.6)
Hypertension (treated)	501 (18.8)	419 (17.9)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Cholelithiasis	304 (11.4)	237 (10.1)	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Hyperlipidaemia	185 (7.0)	153 (6.5)	1.1 (0.9–1.4)	1.1 (0.9–1.4)
Uterine leiomyomas	324 (12.2)	306 (13.1)	0.9 (0.8–1.1)	1.0 (0.8–1.2)
Pelvic inflammatory disease	87 (3.3)	65 (2.8)	1.2 (0.9–1.6)	1.2 (0.9–1.6)
Physician-diagnosed subfertility	46 (1.7)	48 (2.1)	0.8 (0.6–1.3)	0.8 (0.5–1.2)
Ovarian cysts/ benign tumours	128 (4.8)	145 (6.2)	0.8 (0.6–1.0)	0.8 (0.6–1.0)
Menstrual irregularity	204 (7.7)	280 (12.0)	0.6 (0.5–0.7)	0.6 (0.5–0.8)
Benign breast disease	376 (14.1)	194 (8.3)	1.8 (1.5–2.2)	1.7 (1.5–2.1)
Previous breast biopsies	89 (3.3)	33 (1.4)	2.4 (1.6–3.6)	2.2 (1.5–3.3)

*Mantel–Haenszel estimates adjusted for age.
†Estimates from multiple logistic regression equations including terms for medical condition or procedure, age, area of residence, education, age at first birth, menopausal status and, except for severe overweight, body mass index.

Table 3. Relation between history of selected diseases and breast cancer risk, by menopausal status and parity

Diagnosis	Menopausal status				Parity			
	Premenopausal		Post menopausal		Nulliparous		Parous	
	Cases controls*	OR† (95% CI)	Cases controls*	OR† (95% CI)	Cases controls*	OR† (95% CI)	Cases controls*	OR† (95% CI)
Diabetes	18	1.1	107	1.0	16	0.9	109	1.0
	11	(0.5–2.3)	142	(0.7–1.3)	16	(0.5–1.9)	97	(0.8–1.3)
Thyroid disease	95	1.0	135	1.1	51	1.4	179	1.1
	63	(0.7–1.4)	117	(0.9–1.4)	37	(0.9–2.1)	143	(0.9–1.4)
Severe overweight	107	1.0	256	1.4	59	1.5	304	1.2
	82	(0.7–1.3)	181	(1.2–1.7)	38	(1.0–2.3)	225	(1.0–1.5)
Hypertension (treated)	88	0.8	413	1.2	93	1.3	408	1.1
	73	(0.6–1.1)	346	(1.0–1.4)	69	(0.9–1.9)	350	(0.9–1.2)
Cholelithiasis	85	1.3	219	1.1	36	1.0	164	1.2
	48	(0.9–1.9)	189	(0.9–1.4)	35	(0.6–1.6)	202	(1.0–1.5)
Hyperlipidaemia	33	1.1	152	1.1	42	1.2	143	1.1
	22	(0.6–1.8)	131	(0.9–1.4)	34	(0.7–1.9)	119	(0.8–1.4)
Uterine leiomyomas	67	1.2	257	0.9	60	1.0	264	0.9
	41	(0.8–1.7)	265	(0.8–1.1)	55	(0.7–1.5)	251	(0.8–1.1)
Pelvic inflammatory disease	43	1.0	44	1.3	17	1.2	70	1.2
	33	(0.7–1.6)	32	(0.8–2.1)	15	(0.6–2.4)	50	(0.8–1.7)
Physician-diagnosed subfertility	23	0.8	23	0.8	33	1.0	13	0.7
	21	(0.5–1.4)	27	(0.5–1.5)	32	(0.6–1.7)	16	(0.3–1.4)
Ovarian cysts/benign tumours	49	0.9	79	0.7	30	0.8	98	0.8
	45	(0.6–1.4)	100	(0.6–1.0)	36	(0.5–1.3)	109	(0.6–1.0)
Menstrual irregularity	103	0.6	101	0.7	39	0.5	165	0.7
	138	(0.4–0.7)	142	(0.5–0.9)	75	(0.3–0.7)	205	(0.5–0.8)
Benign breast disease	181	1.7	195	1.8	86	2.4	290	1.7
	86	(1.3–2.3)	108	(1.5–2.3)	38	(1.6–3.6)	156	(1.4–2.1)
Previous breast biopsies	50	3.7	39	1.6	22	2.4	67	2.5
	10	(2.0–7.0)	23	(1.0–2.7)	9	(1.1–5.1)	24	(1.6–3.9)

*No. of cases and controls with prior diagnoses.
†Mantel–Haenszel estimates adjusted for age.

Table 4. Timing of diagnosis of hypertension in relation to risk of breast cancer among parous women

Diagnosis	Breast cancer cases (%)	Controls (%)	OR* (95% CI)
No hypertension	1756 (80.1)	1512 (80.1)	1
Hypertension			
Before end of most recent pregnancy	23 (1.1)	17 (0.9)	1.2 (0.6–2.2)
After most recent pregnancy	391 (18.0)	240 (18.2)	1.0 (0.9–1.2)

*Mantel–Haenszel estimates adjusted for age.

instances, it is clear that the finding for history of severe overweight was totally accounted for by a 1.4 fold increased risk in postmenopausal women (95% CI 1.2–1.7), which concurs with no evidence of effect in premenopausal women. Conversely, the positive association with history of breast biopsies seemed to be somewhat stronger in premenopausal women. Such difference did not derive from a higher frequency of breast biopsy in premenopausal women reporting a positive family history for breast cancer. The protection afforded by menstrual irregularities did not vary according to a woman's menopausal status or parity.

Because of the report of a potential protection afforded by hypertension in pregnancy [3], this issue is examined separately in Table 4. However, even considering only hypertension diagnosed before the end of the most recent full-term pregnancy, no difference between breast cancer cases and controls emerged.

DISCUSSION

Our findings, although largely negative, provide in a large data set a quantitative assessment of the role of several medical conditions only anecdotally and sporadically considered in relation to breast cancer risk.

For diabetes mellitus, a correlation between its prevalence and incidence of breast cancer has been reported but was not confirmed by us. The role of thyroid in the development of breast cancer is a question that has been long pursued [17]. A 2-fold increased breast cancer risk after a diagnosis of thyroid cancer emerged from the Connecticut Cancer Registry during 1935–1982 [18]. The reverse was also true and such excesses were particularly evident in women under 40 at diagnosis of first cancer [18]. It was not clear whether such a finding was attributable to some aetiologic factor shared by breast cancer and thyroid cancer (e.g. subfertility) or to close medical surveillance in women with previous cancer diagnosis. However, data from the Danish Cancer Registry during 1943–1980 [19] did not confirm the elevation of breast cancer risk after thyroid cancer. For benign conditions of the thyroid gland, some investigations have shown an increased breast cancer risk among patients with hypothyroidism, autoimmune thyroidism, and hyperthyroidism while others have demonstrated a decreased risk associated with either hypothyroidism or hyperthyroidism [17]. Our negative findings are, however, in agreement with most case-control studies [17] and a few prospective investigations [20] from which a previous diagnosis of thyroid disease was not a risk factor for breast cancer.

The positive association between breast cancer risk and history of severe overweight that indicated medical treatment is consistent with the results of two prospective studies [21, 22] and many, although not all [23], of the case-control studies in which menopause-specific analysis is provided. In a preliminary analysis of the first 1108 breast cancer cases and 1281 controls of the present series [15], the different effect of obesity according to menopausal status emerged less clearly. The widely accepted explanation for such a difference is that severe overweight substantially increases the concentration of total and free oestradiol and oestrone in postmenopausal women but not in ovulating women [1].

De Waard and Baanders-Van Halewijn [14] suggested that high blood pressure might be directly related to the risk of breast cancer among postmenopausal women, while Thompson *et al.* [3], in a case-control study on women below age 55, claimed that hypertension reduced breast cancer risk among parous women if diagnosed before the end of their last pregnancy. Since hypertension during pregnancy is associated with increased levels of maternal α-fetoprotein [3], the hypothesis was made that such exposure may protect against subsequent onset of breast cancer. In the past, most studies with data on breast cancer and hypertension were established to explore the widely debated possibility that reserpine, an anti-hypertensive which enhances prolactin levels, may increase cancer risk [24]. The results of these studies, as well as those of the present analysis, weigh against the possibility of hypertension *per se* playing a role in breast cancer aetiology.

Oestrogens increase the degree of biliary cholesterol saturation and hence the risk of formation of the commonest gallstones among whites (i.e. cholesterol gallstones) [6]. We found a hint that women (particularly those who are premenopausal and parous) who reported a history of cholelithiasis, but not of a potential correlate of it, hyperlipidaemia, may experience some elevation in breast cancer risk.

A history of uterine leiomyomas and pelvic inflammatory diseases was unrelated to breast cancer risk. Similarly, and in agreement with a cohort study [25], no risk elevation was found in those women (less than 2%) who reported to have been diagnosed and treated for subfertility.

Conversely, some protection seemed to derive from previous diagnosis of ovarian cysts and benign tumours. This finding was not accounted for by earlier menopause, as a consequence of more frequent bilateral oophorectomy in women who suffer from ovarian disorders, nor by any difference in reproductive or menstrual characteristics. The interpretation of such a finding is not straightforward since ovarian cysts and benign tumours include several histological entities (e.g. polycystic ovarian diseases, endometriosis, functional cysts) known to share some but not all risk factors with breast cancer [9]. However, the protection conferred by menstrual irregularities, although it does not completely account for the decrease in risk deriving from ovarian cysts and benign tumours, suggests that a higher frequency of anovulatory cycles in women with menstrual irregularities and/or ovarian cyst may be the relevant factor. At variance with what was suggested in the early 1980s [26], there is now evidence that regular ovulatory cycles may increase breast cancer risk, since in the mammary gland mitotic activity appears to be low during the follicular phase and to reach a peak in the luteal phase of the cycle [1]. A prospective study on patients

with well-documented chronic anovulatory syndrome showed that endometrial cancer was the only malignancy significantly increased [27], whereas menstrual irregularities and long cycle length (i.e. lower proportion of menstrual life in the luteal phase) were found more frequently in breast cancer cases compared with controls, or in high-incidence compared with low-incidence populations [28].

Women who reported a positive history of benign breast disease were confirmed to have an approximately 2-fold increased risk of subsequently developing breast cancer. Also in agreement with previous work, such risk elevation seemed to persist for many decades after benign breast diseases had been diagnosed and to vary according to disease severity [29]. The greatest risk elevation was hence found for those lesions that, because of their concerning appearance and/or persistence, required a biopsy.

Our study had unprecedented power to detect small differences (i.e. 90% power of detecting 1.3–1.5-fold increased cancer risk with 5–10% of diseased persons among controls). The hospital-based study design does not seem to have caused selection bias: the prevalence of medical conditions among controls was similar to that found in the Italian National Health Survey, based on 90 000 subjects representative of the whole Italian population [30]. Conversely, for recall bias and data quality, the performance of the interviews in a hospital setting probably assured more complete ascertainment of medical history and a closer similarity between cancer cases and controls compared with that obtainable in a community setting [31]. Cases and controls can similarly recall medical conditions and procedures [31]. Among the strengths of the present study, we had an almost complete participation rate and the possibility of supplementing interview information with medical record data [32], with the consequent minimization of the risk of false negatives.

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