Oral Contraceptive Use: Association with Frequency Of Hospitalization and Chronic Disease Risk Indicators

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Abstract: A questionnaire was mailed to 97,364 married women, aged 26–50, resident in Greater Boston in 1970, requesting information on lifetime oral contraceptive (OC) use, reproductive history, education, and hospitalization experience in 1969; 65,843 women responded. In 1973 a second questionnaire was mailed to 37,292 of these women, including all OC users and an equal number of non-users matched on age, parity, education, and town of residence. This questionnaire related to use of OCs, other female hormones, and the menopause. OC use was most strongly related to age, with a sixfold increase in use from the oldest women (of whom 10 per cent had used OCs at some time) to the youngest. Use was directly related to education and mobility and inversely related to parity. Reasons for beginning and ceasing use differed for women of different ages and educational attainment. Thus, use of OCs varies with social and reproductive characteristics that are risk indicators for many diseases. OC use was associated with increased risk of hospitalization for thromboembolic disease (risk ratio = 1.5, 95 per cent confidence limits 1.2, 3.2) and for mental illness, hyperthyroidism, hypertension, and cancer of the cervix. OC users were hospitalized for many non-life threatening conditions 20 to 40 per cent more frequently than were non-users. (Am. J. Public Health 68:335–341, 1978)

Introduction

Oral contraceptives (OCs) have been widely used for nearly 15 years. Yet, little is known of their health effects beyond their direct association with risk of thromboembolism,[1–3] gall bladder disease,[3] myocardial infarction,[4, 5] and hypertension,[6] and the inverse association with risk of benign breast disease.[7–9] These effects appear soon after use is begun. Effects that develop after prolonged OC use or after a long latent period are unevaluated. It is likely that OCs cause many unknown physiologic alterations.[10, 11] For these reasons, and especially because of an interest in the effect of these agents on the risk of breast cancer, a prospective follow-up study of the health effects of OC use was begun in 1970.

In addition to its follow-up aspects, the study had cross-sectional and retrospective components. Subjects were asked about current and former use of OCs and recent hospitalizations. This paper describes findings from this component of the study. It also describes the relationships between OC use and risk indicators of disease in a large urban population. An understanding of these relationships may enhance evaluation of the health benefits and risks of OC use. Apart from a survey conducted in 1965,[12] little is known about OC use in this country. Subsequent reports[13, 14] were sociologic and have not evaluated health effects.

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Methods

The study population resided in Boston and 14 contiguous towns to the south and west. Nearly all women born 1920–44 and married, as judged from household composition in January 1969, were eligible. Women were identified from Residents' Lists prepared annually by these towns. These Lists contain the name, address, year of birth or age, and occupation of all residents aged 20 and over and are quite complete.[15] Because some Lists gave age rather than year of birth some subjects had been born in 1919. They were retained and are grouped with women born from 1920 through 1924. To facilitate follow-up, women listed in the 25 per cent of Boston precincts with the lowest median family incomes were excluded. Wives of physicians or pharmacists were also excluded.

A questionnaire was sent to 97,364 women. The first mailing occurred in March 1970; non-respondents and persistent non-respondents were solicited again in June 1970 and June 1971, respectively. The information requested was date of birth, number and ages of children, age at completion of formal education, and reason for all hospitalizations in 1969. Women who had never used OCs were asked if a doctor had advised them not to use these agents, and if so whether this was for health reasons. Women who had ever used OCs were asked when they began, whether they were still using them and, if not, when and why they had stopped. Users were also asked to estimate their cumulative duration of use.

Age at completion of education was selected as an index of socioeconomic status (SES) because it can be included in a brief questionnaire without lowering response. This index

misclassified into an upper social class some women for whom late age at completion reflects delayed passage through school rather than high attainment. The probable effect of this is to reduce the strength of any association of OC use with SES.

In March 1973, Phase 2 of the study was begun. A questionnaire was sent to all 18,646 women who responded in Phase 1 stating they had used OCs and for whom all data needed for matching were available, and to an equal number of non-user respondents. Non-users were matched to users for year of birth (1919–24, 1925–34, 1935–44), parity (0, 1–3, 4+), age at completion of education (<19, 19+), and town of residence. Information requested related to hospitalization experience from 1970–1972, change in parity status 1970–1973, OC use 1970–March 1973, use of other female hormones, and menopause history.

Information from both phases of the study is presented. That without specification of origin comes from the 1970 survey (Phase 1). Hospitalization rates per 1,000 woman-years were derived. Except as noted otherwise, age-standardized hospitalization rates or prevalences of OC use were standardized by the direct method to the distribution of all respondents in 5-year age groups. Each risk ratio (RR) is the ratio of the age-standardized hospitalization rate of OC users, or a specified subset of users, to the age-standardized rate for non-users. Throughout this report, "user" designates a woman who had ever used OCs prior to returning her Phase 1 questionnaire, and "non-user" designates all other Phase 1 respondents. For some causes of hospitalization, the RR was estimated for several categories of duration and recency of OC use. A "recent user" is a woman who used OCs during the calendar year prior to hospitalization (i.e., in 1968 for Phase 1). A "former user" is one who had used them only prior to that year. The significance test is the Mantel-Haenszel summary chi-square computed after stratification for the potentially confounding variables mentioned in context.[16]

Results

Response

There were 96,390 (99 per cent) of Phase 1 questionnaires delivered and, of these, 67,563 (70 per cent) were returned. Responses received from 1,720 women outside the eligible age range are excluded from this report. In Phase 2, 81 per cent of questionnaires were delivered, 77 per cent of those sent to users and 85 per cent of those sent to non-users. Among questionnaire recipients, 82 per cent of OC users (11,784 of 14,357) and 78 per cent of non-users (12,357 of 15,849) responded. Young women and women of low parity were overrepresented among subjects whose Phase 2 questionnaire was not delivered.

As expected, because of the inclusion criteria, the education of Phase 1 respondents was somewhat longer than that of the total female population of the same age in the Boston Standard Metropolitan Statistical Area (SMSA). Therefore, most results are given with specification of, or standardization for, age at completion of education.

Parity

Among Phase 1 respondents, the mean number of children was 2.8. Only 7 per cent of these women were nulliparous and 11 per cent uniparous, whereas of all married women aged 25–50 in the Boston SMSA in 1970, 14 per cent were nulliparous and 15 per cent uniparous[17] (rates directly standardized to the age distribution of the respondents). The deficit of women of low parity among respondents is probably due to the high mobility of women of low parity (suggested by the Phase 2 data) causing them to appear in the Residents' Lists after they have moved. There is a marked shift to lower parity as age at completion of education increases. Only 5 per cent of women with the least education were nulliparous compared to 17 per cent of those in the highest educational category (age-standardized percentages). The mean age at first birth for parous respondents is 25 years.

Oral Contraceptive Use

Of Phase 1 respondents, 30 per cent (19,682 women) had used OCs at some time (a further 6 per cent of 1970 non-users had used OCs by 1973). There was a higher percentage of OC use in successive birth cohorts as shown in Figure 1. The distribution of duration of OC use is depicted in Figure 2, which indicates that women who had used OCs for some years in 1970 were likely to continue using them in sub-

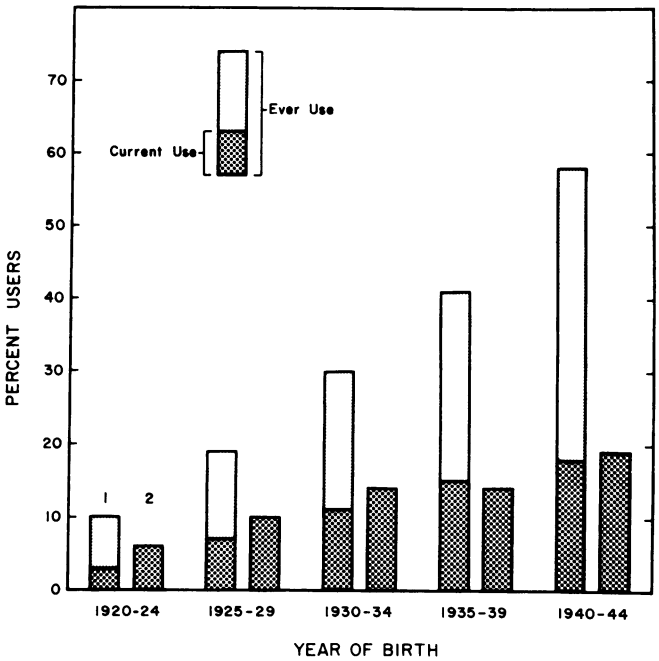

FIGURE 1—Oral contraceptive use according to year of birth. Percentage of ever users in 1970 and current users in 1970 and 1973. Phase 1 figures based on all responses in 1970: Phase 2 current use based on all responses in 1973.

1 = Phase 1 (1970)

2 = Phase 2 (1973)

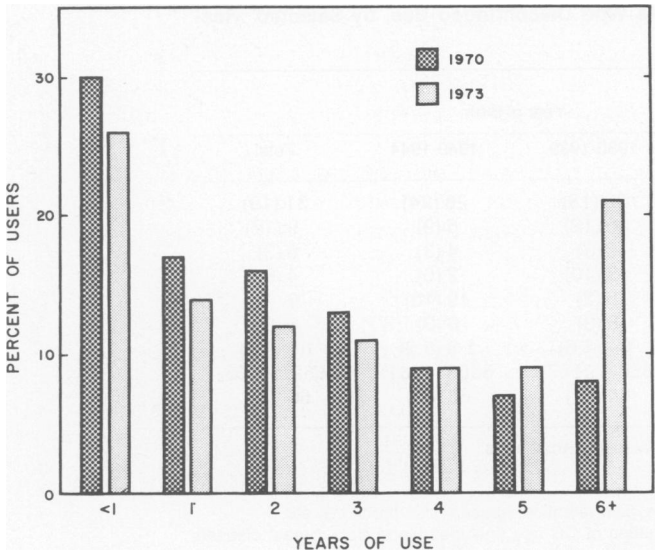

FIGURE 2—Duration of OC use for all users.

1970—19,682 respondent users

1973—12,483 respondent users (including those who started post-1970)

sequent years. 6,712 women were using OCs when they completed the Phase 1 questionnaire; this gives an overall current use rate in 1970 of 10 per cent (12 per cent in 1973), with little difference between socioeconomic groups. Only 3 per cent of women born in 1920–24 were current users (6 per cent in 1973) compared with 18 per cent of the 1940–44 cohort (19 per cent in 1973). This trend was seen at each educational level.

Within each birth cohort, the frequency of having ever used OCs rose with increasing education. This varied from a low of 8 per cent for women born from 1920 to 1924 and who completed their education prior to age 17, to a high of 70 per cent for women born from 1940 to 1944 and who completed their education after age 22. After standardization for age and education, mobility was also related directly to OC use.

Thirty-five per cent of nulliparous women had used OCs. This declined regularly with increasing parity to 25 per cent for women with six or more children. However, when this relationship is examined in age and education subgroups, it appears that the inverse trend with parity results from the pattern in the groups with very high percentages of OC users, i.e., the younger and the more educated women. In fact, there is an opposite trend, more frequent use among women of higher parity, among older or less well-educated women.

Overall, OC use among parous women declined as age at first birth increased. Forty-two per cent of women who delivered their first child prior to age 20 had used OCs, compared to only 25 per cent of those who were age 25 or older. The trend is most evident for younger women of lesser education.

TABLE 1—Per Cent Distribution of Users by Reason[1] for Starting Oral Contraceptives, by Birth Cohort and Age at Completion of Education (Phase 1 data).

Year of Birth	Reasons for Starting[2]	Age at Completion of Education <19	19-20	21+
1920-29	Delay	4	4	6
	Space	13	12	13
	Terminate	82	82	79
1930-39	Delay	5	11	20
	Space	28	28	30
	Terminate	66	60	44
1940-44	Delay	22	41	71
	Space	39	35	20
	Terminate	39	24	8

[1] See text for method used to allocate women to the differing reasons. Percentages do not add to 100 in most groups because some women could not be classified as to reason for starting.

[2] Delay = to delay a first birth
Space = to space successive births
Terminate = to terminate reproduction

The differences in OC use between birth cohorts and educational groups might reflect different reasons for starting OC use. Therefore each user was classified as to whether she began using OCs prior to the birth of her first child, between her first and last child or after her last child. These categories are construed as characterizing women as first using OCs either to *delay* or prevent a first birth, to *space* children, or to *terminate* childbearing.* When all OC users are so classified, the distribution by year of birth and education is as given in Table 1. There are two marked tendencies: 1) A clear trend from beginning OC use to terminate reproduction to beginning OC use to delay or space children, as one moves from the oldest to the youngest women. This may be partly explained by the unavailability of OCs to older women in their early reproductive years. It is consistent in each education group; 2) An equally strong tendency towards a greater percentage of first use to delay a first birth as education increases.

Discontinuation of Oral Contraception

Of the 19,682 women who had ever used OCs by 1970, 12,970 (66 per cent) had stopped prior to responding to the questionnaire. Selected reasons for discontinuing OCs are listed in Table 2. A woman was counted in categories where her first two stated reasons for stopping applied, and could thus be included once or twice in Table 2.

Differences between educational groups were noted in only three of the categories of reasons for stopping for both

*Women first using OCs after their first child but who had not had a second child were assigned to the "spacing" category. Since many women are still in their reproductive years, there will be some reclassification from the "spacing" to the "terminating" category. The distinction between "delay" and the other categories is permanent.

TABLE 2—Per Cent of All OC User Respondents Who Discontinued Use, by Selected° Reasons, According to Birth Cohort.

Reason for stopping[1]	Year of Birth			
	1920-1929	1930-1939	1940-1944	Total
Side Effects	33* (16)+	32 (18)	28 (24)	31 (19)
Medical	12 (17)	10 (12)	6 (9)	9 (12)
Medical Use	8 (4)	6 (3)	4 (3)	6 (3)
Other Methods	7 (8)	3 (10)	2 (6)	4 (8)
Children	0.7 (0.1)	5 (2)	19 (10)	9 (4)
Publicity	7 (2)	8 (3)	0 (3)	8 (3)
Break	1.2 (2.7)	1.4 (4.6)	1.8 (3.3)	1.5 (3.8)
Total Number of Users	4209 (1244)	8562 (2887)	6888 (1931)	19,659[2] (6062)
Per Cent Stopped[3]	67 (53)	64 (61)	68 (53)	66 (52)

° Selected because of size of group or interesting trend across birth cohorts.
* Phase 1 results
+ Phase 2 results in brackets
[1] Side Effects: includes emotional problems, weight gain, fluid retention, nausea, skin problems, etc.
Medical: medical conditions which required discontinuation of OC use (includes blood clots, breast disease, liver abnormality, hypertension and heart disease, vaginal bleeding, and thyroid disease).
Medical Use: had used OCs for medical reason only (eg. to regulate menses).
Other Methods: changed to other contraceptive methods (includes women who underwent hysterectomy).
Children: desire to become pregnant.
Publicity: fear of side effects a woman had read or heard about.
Break: to take a break from medication or because of change in sexual activity.
[2] 23 OC users whose year of birth is unknown are excluded.
[3] Although not all categories of reasons for stopping are included, this figure may be less than the sum of the individual percentages since women could be included more than once.

Phase 1 and Phase 2 (Table 3). The direct association of amount of education with ceasing OC use to become pregnant corroborates the earlier analysis of reasons for starting OC use in the different educational groups: that is, women with little education are less apt to stop contraception in order to conceive because, it appears, they began using OCs to terminate reproduction.

The Phase 2 data are also presented in Tables 2 and 3, and generally show the same trends, although the actual frequencies are rather different.

Use of Female Hormones other than OCs

There were 3,495 women (15 per cent of Phase 2 respondents) who reported use of other female hormones at some time. Little difference in use was apparent by OC user status or between socioeconomic levels, but 37 per cent of women in the 1920-24 birth cohort used these hormones, compared with 8 per cent born in 1940-44. This presumably reflects treatment for peri-menopausal symptoms in the older women.

Recently, there has been an increased use of female hormones in all birth cohorts, with over one-half of all users beginning in 1968 or later. The cohort-specific increases are seen for all education categories except the highest (age at completion of education 26+). There have been reports of an association between the use of conjugated oestrogens and endometrial cancer.[18–20] If these are valid, the present data suggest that incidence rates of this disease will rise over the next few years. Indeed, such a rise has already been reported.[21]

Operative Menopause

There were 3,487 women (14 per cent of Phase 2 respondents) who had stopped menstruating by March 1973. Of these, 2,247 (64 per cent) had had an operative menopause. This high prevalence is due to the relatively low age of the study cohort; their prevalence of natural menopause will be low for some years yet (see Table 4).

Hospitalization Experience

Hospitalization rates (Phase 1) for selected conditions for women who ever had used and those who never had used OCs appear in Table 5. These are all conditions for which the

TABLE 3—Per Cent Distribution of Women Who Stopped Using Oral Contraceptives According to Selected Reasons, by Age at Completion of Education.

Reason for Stopping[1]	Age at Completion of Education				
	<17	17, 18	19, 20	21+	Total
Children[2]	4* (3)+	6 (3)	9 (3)	15 (7)	9 (4)
Publicity[3]	6 (1.1)	8 (2.2)	9 (2.9)	10 (3.5)	8 (3)
Pregnancy	0.7 (0.8)	0.5 (0.2)	0.6 (0.4)	0.3 (0.1)	0.5 (0.2)

* Phase 1 results
+ Phase 2 results
[1] As for Table 2 (Pregnancy: became pregnant while taking oral contraceptives).
[2] Trend seen only in women under 40 for Phase 1 data.
[3] Trend more marked in women under 35 for Phase 2 data.

TABLE 4—Natural and Operative Menopause in Phase 2 Respondents, by Birth Cohort.

	Year of Birth					
	1920-24	1925-29	1930-34	1935-39	1940-44	Total
Number ceased menstruating by 1973	1245	1199	575	339	129	3847
Per cent ceased menstruating among total birth cohort	57	25	12	5	2	14
Number with operative menopause	449	889	520	294	95	2247
Per cent of all menopausal women with operative menopause	36	74	90	87	74	64

rates differed significantly at the 5 per cent level. Hospitalization rates of non-users, for most conditions, are similar to those reported in a 1965 National Survey.[22]

The risk ratio (RR) estimates obtained are probably biased in favor of apparent "protection" for OC users with respect to illnesses for which OCs are contraindicated. For example, low RRs obtained for diabetes (0.6) and breast cancer (0.8) may result because women having, or at high risk of developing, such conditions are unlikely to receive OCs. Indeed, when non-users who stated they did not use OCs because they were so advised by a physician are removed from the comparison, the RRs are increased to 1.3 for diabetes and 0.9 for breast cancer. Despite this bias, most RRs suggest increased risk for users. They have a 20 per cent or greater increase in hospitalization rates even for conditions unlikely to be related biologically to OC use, such as appendectomy (p = .07), oral surgery (p = .10), trauma (p = .07), and "lab tests." Controlling for socioeconomic status as well as age removes most of the apparent excess risk of hospitalization for trauma (RR = 1.1, previously 1.4), but RRs for the other conditions are virtually unchanged.

TABLE 5—Hospitalization Rates: Year Prior to Phase 1 Response (selected conditions*)

	Rates+		Risk Ratio
	Users	Non-users	
Increased in OC ever-users			
Cancer of Cervix	0.5	0.1	5.0
Hypertension	1.0	0.3	3.3
Mental Illness	2.7	1.4	2.0
"Lab tests"	4.9	2.9	1.7
Thromboembolism	2.0	1.3	1.5
Hysterectomy	16.7	11.0	1.5
Gall-bladder Disease	5.3	4.6	1.2
Increased in never-users			
Childbirth	65.9	82.9	0.8
All admissions			
TOTAL	203.8	189.8	1.1
TOTAL less childbirth	137.9	106.9	1.3

*Selected because rates differ significantly ($P < .05$ except for thromboembolism, where $P = .06$).

+ Annual rate per 1,000, age-standardized.

Cancer of the cervix and hypertension are conditions for which users have an increased risk greater than the probably artefactual 20 to 40 per cent excess. Further analysis reveals little alteration in the risk of cervical cancer with months of OC use or recency of use, and the RR is unchanged when parity, as well as social class, is controlled. The rate of hospitalization for hypertension increases with longer durations of use [<16 months use, RR = 0.5 (with 95 per cent confidence limits of 0.3, 3.9), 16+ months use, RR = 5.5 (2.1, 10.9)]. There is also a slight trend towards greater risk with more recent use (former user, RR = 2.4, (0.5, 6.5); recent user, RR = 4.0 (1.0, 5.4)). Hyperthyroidism may also occur in excess among users, RR = 3.0, but the hospitalizations for this condition are too few (five) to permit any statistically sound conclusion to be drawn.

The role of OCs in the etiology of thromboembolic disease is established.[1-3, 10, 11] The RR noted here, 1.5 (1.2, 3.2) is much lower than that found in earlier studies. The discrepancy may be due to the restriction of prior studies to "idiopathic" thromboembolism while the present study includes all cases. This can be evaluated: it seems likely that most cases among the youngest women (ages 25-29) in our population would be idiopathic. In fact, the RR for users in this age group is 5.0 (95 per cent one-sided lower confidence bound of 1.8 based on a rate of 2.0 per 1,000 users per year and a rate of 0.4 for non-users), an estimate similar to earlier reports. In addition, in this age group, the risk is even higher among women using OCs at the time of diagnosis. There is no association of risk with duration of use among recent users. Both of these observations are similar to those reported previously.

The RR of 2.0 for hospitalization for mental (including "emotional") illness is based on reasonable numbers of hospitalizations. There is no trend in the risk with duration of use, but excess risk is nearly absent for women who have used OCs for 40 months or longer. There is also little variation in risk with recency of OC use; women who had stopped more than a year ago having a risk only slightly higher than that of more recent users.

The low hospitalization rate for benign breast disease among OC users is similar to that noted in case-control studies[3-5, 9, 23] and one cohort study.[24] Trends in rates by age and by duration and recency of use are consistent with those already reported. As the relevant data from the prospective component of this study have already been published[25] detailed analyses are not presented. However, the data in Table 6, from the retrospective part of the study, are suggestive of a relationship with duration of use.

Analysis of Phase 2 data (hospitalization experience 1970-1972 by OC user status prior to 1970) provided RR estimates consistent with those presented for Phase 1 with the exception of cancer of the cervix, where the RR for OC use was only 1.8 (based on 11 cases).

TABLE 6—Rates, Risk Ratio and Numbers of Cases of Benign Breast Disease (in parenthesis) by Duration of Oral Contraceptive Use (Phase 1).

	Months of OC use				
	Non-users	1-9	10-15	16-39	40+
Rate	5.4 (268)	6.4 (28)	6.0 (9)	3.1 (23)	3.1 (14)
Risk ratio	1.0	1.2	1.1	0.6	0.6

Discussion

The present study differs from previous investigations both in its size and in its near-total coverage of a general population, as well as in its orientation towards health rather than sociological issues. It is thus reassuring to see that, for the most part, the present results corroborate and extend the findings of prior investigation.

(a) OC use and risk indicators of disease. OC users differ from users of other means of contraception with respect to characteristics relevant to disease experience.[12, 26–28] Here that concept is extended to point out that OC users are themselves a heterogenous group with regard to risk indicators for many diseases. Such strong determinants of disease experience as age and SES were associated with different OC use patterns for women who were similar with respect to other important disease risk indicators such as parity and age at first birth. In moving from older to younger age groups or from the lesser to the more educated there was a tendency from first using OCs to terminate reproduction to first using them to delay a first pregnancy. This has implications for the study of diseases related either to the onset or frequency of reproduction. For example, if, as has been proposed,[29, 30] risk of breast cancer is related to hormonal patterns in young adulthood, then any effect of OC use on breast cancer risk might be noted first among younger women. Practically, this implies that studies of OC-breast cancer associations among older women may not be informative.

There are public health implications of these patterns independent of any direct health effects of OC use. Again, using the breast cancer example, women already at some increased risk of breast cancer—those of higher socioeconomic class—are using OCs in a manner that moves them into a higher risk group for a major risk indicator, age at first birth.

The historical or sociological reasons for some of the observed variations in OC use may be obvious, e.g., for birth cohort and educational differences. Since the differences in OC use by birth cohort are undoubtedly due to the recent availability of these agents, women of subsequent birth cohorts would be expected to be more alike as they will have had the opportunity to use OCs throughout reproductive life. However, the increasing use of vasectomy and tubal ligation makes it impossible to predict future OC use patterns.

(b) OC use and hospitalization experience. There may be differential hospitalization practices for OC users and non-users that are unrelated to effects of the medication itself. There are at least three ways in which such bias might occur. First, OC users may be over-utilizers of medical care in general and are at increased risk of elective hospitalization compared to non-users. Some of our findings support this idea, particularly the increased risk of hospitalization for oral surgery, pneumonia, and laboratory tests. If a hospitalization bias is what these associations indicate, it should be noted that the bias increased rates by 20 to 40 per cent. Second, OC users may be at increased risk of hospitalization for conditions which are known or suspected to be caused by OCs. Again, this may not relate to any effect of the hormones but to the high index of suspicion for these conditions in users. The finding on cervical cancer may result from this. A third way in which hospitalization bias may occur is that OC users may remember and report their hospitalization better than do non-users. A general excess in hospitalization rates for users may cause case-control studies which use as controls hospitalized women, to underestimate the true strength of associations between OC use and conditions which such use causes.

In the face of bias in favor of hospitalization among OC users the finding of their lower rates of hospitalization for benign breast disease appears valid. On the other hand, a false "protective" effect would be produced if OCs are withheld from women considered at high risk of benign breast disease. However, exclusion of women who stated that they did not use OCs because of medical advice, though a limited control for this difficulty, did abolish the protective effect initially noted for breast cancer and diabetes, but did not reduce that for benign breast disease.

The positive association of OC use with cervix cancer risk, reported here and previously, may be non-causal. In discussing a study[31] showing a high prevalence of *in situ* cancer of the cervix among women using OCs, Doll mentioned three possible explanations: OCs cause carcinoma *in situ*; the use of a diaphragm protects against the disease; or women who select OCs are more likely, for other reasons, to develop the lesion.[10] The present study does not support or refute any of these explanations. Other data support the last two explanations.[27, 32–34]

The problem of whether OC use contributed to the condition or whether the condition leads to OC use is pertinent to the association with hospitalization for mental illness. In light of speculation about depressive effects[35, 36] this association certainly warrants further attention.

The associations with hyperthyroidism and hypertension are noteworthy in light of theoretical considerations, previous case reports, and clinical series.[6, 37–40] The trends noted for these associations indicate a need for further evaluation.

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