Oral Contraceptive Use and Mortality during 12 Years of Follow-Up: The Nurses' Health Study

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■ *Objective:* To examine prospectively the risk for mortality among women who had ever used oral contraceptives compared with those who had never used oral contraceptives.

■ *Design:* Prospective cohort study.

■ *Setting:* Nurses' Health Study.

■ *Participants:* 166 755 women aged 30 to 55 years in 1976, followed through 1988 (1.3 million person-years of follow-up).

■ *Results:* On the basis of 2879 deaths, we found no overall difference in mortality among women who had ever used oral contraceptives compared with women who had never used oral contraceptives; the relative risk for ever-users, adjusted for age, body mass index, and cigarette smoking was 0.93 (95% CI, 0.85 to 1.01). We observed no trend in risk for total mortality with increasing duration of past use of oral contraceptives. After adjusting for age, body mass index, and cigarette smoking, women who had used oral contraceptives for 10 or more years had a relative risk of 1.06 (CI, 0.83 to 1.35).

■ *Conclusion:* Use of oral contraceptives is safe; no evidence from this study indicates that long durations of oral contraceptive use adversely affect long-term risk for mortality.

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The use of oral contraceptives has become widespread. Over 50 million women in the United States have used oral contraceptives since their introduction in 1960 (1). Oral contraceptives clearly reduce the risk for ovarian cancer (2) and endometrial cancer (3, 4), and current use increases risk for myocardial infarction, stroke, venous thromboembolism, and hepatocellular carcinoma. The overall association with breast cancer remains unclear; some increase in risk with use early in life has been suggested (5), but no strong overall association beyond the increase in risk seen among current users has been observed (6, 7). Previous attempts to document the balance of long-term risks and benefits of oral contraceptives have combined data from independent studies of different end points (8, 9) or, alternatively, have been based on follow-up of cohort studies (10–12).

Although synthetic decision or risk-benefit analyses derived from several individual studies can provide a useful estimate of the range of possible overall effects, some risks or benefits may not be included. To estimate the effect of oral contraceptives on total mortality, risk-benefit analysis is most frequently used, although such analyses may not be optimal to assess mortality, particularly if most studies address relations between exposure such as oral contraceptives and disease incidence. Further, although individual studies may provide estimates of risk or benefit, finding a common metric to combine these data is not always intuitively obvious. In addition, differences among studies in the age structure of the study population, the prevalence and distribution of oral contraceptive use, and the prevalence of effect-modifiers such as cigarette smoking and parity may make it inappropriate to combine results across studies.

Data on total mortality have been reported from the follow-up of two cohorts of women in the United Kingdom (4, 12), but each had relatively few deaths (fewer than 250 each), limiting the statistical power for either overall or cause-specific analyses.

In 1976, the Nurses' Health Study was established, with one of its major objectives being to examine the associations between the use of oral contraceptives and risks for major illnesses. We report data based on 12 years of follow-up for mortality, placing particular emphasis on women who had ever used oral contraceptives and duration of use, in relation to cause-specific and total mortality.

Methods

The Nurses' Health Study Cohort

The Nurses' Health Study cohort was established in 1976, when 121 700 female registered nurses 30 to 55 years of age completed a mailed questionnaire requesting information about risk factors for cancer and cardiovascular disease, including current contraception, previous use of oral contraceptives (including start and stop dates for each episode of use), current and past smoking habits (including number of cigarettes smoked), past history of breast cancer or myocardial infarction, angina, cancer, diabetes, hypertension, high serum cholesterol levels, menopause, and parental history of myocardial infarction. In addition, questions were included on height, weight, use of postmenopausal hormones, and reproductive history including age at menarche, parity, age at first birth, and age at menopause. Since 1976, follow-up questionnaires have been mailed every 2 years to update information on contraception, smoking habit, other cardiovascular and cancer risk factors, and the occurrence of major illness. Further details of the Nurses' Health Study have been described elsewhere (13).

Exposure Data

Women were categorized according to their reported use of oral contraceptives up to 1976 as never-users or ever-users. For ever-users, we calculated time since first use. Based on data reported on the 1976 questionnaire, we classified women as current or past users and calculated the duration of use. For

past users in 1976, we calculated time since last use and past duration of use.

Because the focus of this analysis is on mortality and because women tend to stop using oral contraceptives after they are diagnosed with major illnesses, we have not updated information on current use during the 12 years from 1976 to 1988. Of the 7136 women who were currently using oral contraceptives at the time of return of the 1976 questionnaire, 28% were still current users in 1978, 12% remained as current users in 1980, and 5% were current users in 1982 (357 women). Further, only 70 never-users in 1976 began using oral contraceptives by 1978, and 365 women who were past users in 1976 reported current use of oral contraceptives in 1978. Overall, this yields approximately 21 500 person-years of observation among women who were using oral contraceptives in 1976.

Cigarette smokers were classified in 1976 as never-smokers, current smokers, or former smokers. Current smokers were further classified as using 1 to 14, 15 to 24, 25 to 34, or 35 or more cigarettes per day. Cigarette smoking status was updated with every follow-up questionnaire. Body mass index (weight in kg divided by the square of height in cm) was calculated based on the reported weight and height from the 1976 questionnaire.

Ascertainment of End Points

The end points for these analyses comprised deaths from all causes occurring after the 1976 questionnaire was returned but before 1 June 1988. The deaths were further grouped into broad categories: total cardiovascular diseases (ICD 8th revision codes 410 to 440 and 795 [sudden death]); total cancers (ICD 8th revision codes 140 to 207); accidental deaths and suicide (all "E" codes); and other deaths.

The mortality surveillance included systematic searches of the vital records of the states and the National Death Index to discover deaths among women who did not respond during each questionnaire cycle. This search was supplemented by reports from next of kin and postal authorities. We estimate that over 98% of the deaths in the cohort were ascertained by these methods (14).

The classification of individual causes of death was done by physician review of death certificates. Deaths caused by cancer, cardiovascular disease, and external injury were classified as confirmed if these were listed as the underlying causes on the death certificate. We excluded from analysis all women who had reported angina, myocardial infarction, stroke, and cancer (other than nonmelanoma skin cancer) at baseline because these women are at increased risk for mortality and their use of oral contraceptives may have been terminated after the diagnosis of the incident disease. Further, current practice is not to initiate use of oral contraceptives in women with these conditions. A total cohort of 116 755 women was available for follow-up.

Statistical Analysis

The present analyses included 12 years of follow-up data (1976 to 1988). The primary analysis used incidence rates with person-months of follow-up as the denominator. For each participant, person-months were allocated according to the 1976 exposure variables and updated every 2 years for time since first use and time since last use as indicated above.

Relative risks were calculated as the rate of death in each category for use of oral contraceptives divided by the corresponding rate in the reference category (never-users). All relative risks were age-adjusted by 5-year intervals, and 95% CIs were calculated (15). We also used proportional hazards models to control simultaneously for age, cigarette smoking, body mass index, and other risk factors for cancer and cardiovascular disease. We repeated multivariate analyses for cancer mortality, controlling for established breast cancer risk factors, including age at menarche, parity, age at first birth, and menopause.

Results

For 1.4 million women-years of follow-up, we observed 2879 deaths. In 1976, 55% of women reported that they had used oral contraceptives at some time and 5% reported that they were currently using oral contraceptives. Among users of oral contraceptives, 30% had used them for less than 1 year. The mean and median durations of use as of the return of the 1982 questionnaire (when less than 1% of ever-users remained as current users) did not differ materially by age; the median ranged from 39 months among women born from 1926 to 1930 to 36 months among women born from 1936 to 1940. During the 12 years of follow-up, 568 women died of cardiovascular causes, 1456 of cancer, 114 of suicide, 151 of other traumatic causes of death, and 590 of other causes.

Table 1. Ever-Use of Oral Contraceptives and Relative Risk for Mortality during 12 Years of Follow-up

Relative Risk	Oral Contraceptive Use	
	Never (740 531 Person-Years)	Ever (676 317 Person-Years)
Total mortality		
Cases, *n*	1906	973
Relative risk	1.0	0.99 (0.91 to 1.07)
Multivariate relative risk*	1.0	0.93 (0.85 to 1.01)
Cardiovascular disease		
Cases, *n*	403	165
Relative risk	1.0	0.88 (0.72 to 1.06)
Multivariate relative risk*	1.0	0.86 (0.71 to 1.05)
Cancer		
Cases, *n*	966	490
Relative risk	1.0	1.01 (0.90 to 1.14)
Multivariate relative risk*	1.0	0.92 (0.81 to 1.03)
Suicide		
Cases, *n*	55	59
Relative risk	1.0	1.34 (0.90 to 2.01)
Multivariate relative risk*	1.0	1.32 (0.87 to 1.98)
Other trauma		
Cases, *n*	81	70
Relative risk	1.0	1.29 (0.90 to 1.84)
Other death		
Cases, *n*	401	189
Relative risk	1.0	0.90 (0.75 to 1.08)

* Multivariate adjustment for age (5 years), cigarette smoking (never, past, and current [1 to 14, 15 to 24, 25 to 34, and 35+ cigarettes/d]), body mass index (in quintiles), and follow-up interval. Ninety-five percent CIs are shown in parentheses for all relative risks.

Ever-Users of Oral Contraceptives

We found no overall difference in total mortality among women who had ever used oral contraceptives compared with women who had never used oral contraceptives; the age-adjusted relative risk for women who had used oral contraceptives was 0.99 (CI, 0.91 to 1.07). The magnitude of the relative risk did not differ across age strata except for ages 30 to 34 years where a high proportion of the women were current users, and the relative risk for mortality was 6.9 (based on 25 deaths; CI, 1.2 to 38.6). These deaths included 6 caused by cardiovascular disease; 7 caused by cancer; 5 due to suicide, 3 caused by other trauma; and 4 due to other causes. In the total cohort, mortality among ever-users caused by cardiovascular disease, cancer, and suicide did not differ statistically from that among never-users (Table 1). Adjustment for cigarette smoking and body mass index, known contributors to total mortality, re-

duced the magnitude of association for these overall results. The multivariate adjusted relative risk for ever-users compared with never-users was 0.93 (CI, 0.85 to 1.01).

When we examined the associations with specific causes of cardiovascular and cancer mortality, we found that risk for death caused by coronary heart disease was lower (although not statistically) among ever-users of oral contraceptives, and stroke mortality was not associated with use. These associations did not differ meaningfully when we examined mortality in ever-users within strata of cigarette smoking (never, past, and current smokers of 1 to 14, 15 to 24, and 25 or more cigarettes per day). Again, adjustment for cigarette smoking and body mass index did not materially alter these results (Table 2).

We found no significant association between use of oral contraceptives and cancer mortality. Compared with never-users, the relative risk for women who had ever used oral contraceptives was 1.01 (CI, 0.90 to 1.14). Adjustment for cigarette smoking and body mass index reduced this relative risk to 0.92 (CI, 0.81 to 1.03). Mortality caused by breast cancer was not elevated among ever-users of oral contraceptives compared with never-users (relative risk, 1.07; CI, 0.86 to 1.34), and endometrial uterine cancer mortality showed an apparent but nonsignificant reduction (relative risk, 0.33; CI, 0.10 to 1.11) (Table 3). For other cancers combined, we observed no overall association (relative risk, 0.97; CI, 0.85 to 1.12). These associations between oral contraceptives and mortality from cancer were unchanged when we adjusted for parity, age at first birth, age at menarche, and age at menopause in addition to age, body mass index, and cigarette smoking. Further, the association between oral contraceptives and breast cancer was unchanged when we added family history of breast cancer to the multivariate model.

Current Users in 1976

To further understand the association observed for ever-use of oral contraceptives and cancer mortality, we examined risk among women who were using oral contraceptives in 1976 and their mortality rate during the subsequent 12 years of follow-up. Compared with never-users, women who were using oral contraceptives in 1976 had a significantly increased risk for subsequent breast cancer mortality (relative risk, 1.63; CI, 1.07 to 2.49). This is consistent with the increased risk for breast cancer incidence and the later stage at diagnosis observed among current users as previously reported in this cohort (16). The elevation in relative risk was stable across age strata. Adjusting for age at menarche, parity, age at first birth and at menopause, in addition to age, smoking, and body mass index did not alter this result (adjusted relative risk, 1.67; CI, 1.09 to 2.57). Users of oral contraceptives in 1976 were not at elevated risk for total cancer mortality during the subsequent 12 years, however, compared with never-users, in part reflecting the inverse association for some other cancers.

Total cardiovascular mortality neither increased nor decreased among users of oral contraceptives (relative risk, 0.99; CI, 0.62 to 1.60). There was, however, a suggestion of reduced risk for ischemic heart disease mortality and increased stroke mortality among women using oral contraceptives in 1976, although it was based on small numbers of deaths (Table 4). When we examined subarachnoid hemorrhage (70 deaths), we observed a possible elevation in risk that was not statistically significant (multivariate relative risk, 1.89; CI, 0.77 to 4.65). Overall, women using oral contraceptives in 1976 had a modest, but not statistically significant, increase in risk for total mortality during the subsequent 12 years (relative risk, 1.18; CI, 0.97 to 1.44).

Past Duration of Use

We observed no trend in risk with increasing duration of past use for total mortality or mortality related to cardiovascular disease or cancer. After adjusting for age, body mass index, and cigarette smoking, women who had used oral contraceptives for 10 or more years were not at increased or decreased risk for mortality (relative risk, 1.06; CI, 0.83 to 1.35; Table 5).

Among women who had used oral contraceptives for 10 or more years, we observed an increase in cardiovascular mortality (relative risk adjusted for smoking and body mass index, 1.60; CI, 1.10 to 2.33). Further adjustment for a history of high blood pressure, high cholesterol levels, a family history of heart disease, and a personal history of diabetes reduced this relative risk to 1.43 (CI, 0.98 to 2.09). Nine of the 19 observed deaths in this category were caused by stroke. Women who used oral contraceptives for 10 or more years were not at increased risk for death from cancer compared with never-users; the adjusted relative risk was 0.80 (CI, 0.59 to 1.09).

Time since First Use and Time since Last Use

When we examined the relation between time since first use of oral contraceptives and risk for mortality, we observed no material relation with total mortality, cardiovascular mortality, or cancer mortality.

Table 2. Ever-use of Oral Contraceptives and Relative Risk for Cardiovascular Mortality during 12 Years of Follow-up

Cause of Death	Cases, *n*		Age-adjusted Relative Risk	Multivariate Relative Risk*
	Ever	Never		
Coronary heart disease	85	261	0.82 (0.66 to 1.02)	0.79 (0.61 to 1.03)
Stroke	58	97	1.05 (0.75 to 1.45)	1.03 (0.73 to 1.46)
Other heart disease	21	43	0.95 (0.56 to 1.61)	0.82 (0.46 to 1.44)

* Multivariate adjustment for age (5-year), cigarette smoking (never, past, current 1–14, 15–24, 25–34, 35+ cigarettes per day), body mass index (quintiles), and follow-up interval. 95% CIs are shown in parentheses.

Table 3. Ever-Use of Oral Contraceptives and Relative Risk for Cancer Mortality during 12 Years of Follow-up

Type of Cancer	Cases		Adjusted* Relative Risk	Multivariate† Relative Risk
	Ever-Use	Never-Use		
Breast	153	225	1.07 (0.86 to 1.34)	1.09 (0.87 to 1.36)
Endometrium	3	24	0.33 (0.10 to 1.11)	0.34 (0.10 to 1.17)
Ovary	45	99	0.79 (0.54 to 1.16)	0.81 (0.56 to 1.19)

* Adjusted for age (5 years), smoking (never, past, current 1 to 14, 15 to 24, 25 to 34, and 35+ cigarettes/d), body mass index (in quintiles), and follow-up interval. All relative risks show 95% CIs in parentheses.

† Adjusted for covariates as in *, plus parity (nulliparous, 1, 2, 3+), age at menarche (<13, 13, 14, 15+ years), age at first birth (<22, 23–26, 27+ years), and menopause.

To understand the change in risk after stopping use of oral contraceptives, we next examined the risk for mortality according to time since last use among the women who were past users in 1976. For total mortality, we observed no overall trend between time since last use and risk for death ($P > 0.2$). Women who had used oral contraceptives within the past 5 years were not at elevated risk for mortality from all causes (116 deaths; relative risk, 1.10; CI, 0.89 to 1.35), from cardiovascular disease (21 deaths; relative risk, 1.11; CI, 0.70 to 1.75), or from cancer (47 deaths; relative risk, 0.94; CI, 0.68 to 1.30) when compared with never-users.

Other Causes of Death

We observed 10 deaths caused by primary liver or biliary tract cancer during the 12 years of follow-up (two cases among women who had used oral contraceptives). Ever-use of oral contraceptives was not related to increased risk for liver cancer mortality (age-adjusted relative risk for ever-users was 0.43; CI, 0.08 to 2.42). We observed 71 deaths caused by cirrhosis, 33 deaths caused by diabetes, 31 deaths caused by pulmonary embolism, and 29 unexplained deaths. Overall, the age-adjusted relative risk for mortality for all other causes combined was 1.03 (CI, 0.74 to 1.45) for ever-users compared with never-users. For death caused by pulmonary embolus, the age-adjusted relative risk for ever-users was 1.12 (CI, 0.54 to 2.30) when they were compared with never-users of oral contraceptives.

Discussion

These data, based on more than 2800 deaths, show no appreciable increase or decrease in total mortality among women who have ever used oral contraceptives, although the duration of use by many women in this cohort was relatively short. Despite this lack of overall association, important adverse effects on breast cancer mortality and reduced risk for mortality from ovarian and endometrial cancer were noted. These associations balance when total cancer mortality is considered, in part because the reduced risk for ovarian cancer persists after cessation of use, whereas the apparent excess risk for breast cancer is largely limited to current users. A similar balance is noted for women who used oral contraceptives for 10 or more years; an increase in risk for cardiovascular mortality was balanced by a decrease in cancer mortality.

Follow-up rates in this cohort were high (over 88% of women answered the 1988 questionnaire), and mortality surveillance is almost complete. The National Death Index supplements reports of death by next of kin and the postal authorities; thus, we estimate that more than 98% of deaths are identified. Loss to follow-up or under-ascertainment of deaths is unlikely to have biased these results.

To control for potential confounding, we repeated analyses that included various established risk factors for specific causes of death, such as breast cancer and myocardial infarction. In these detailed analyses, the cause-specific mortality results remained unchanged. Thus, we are unlikely to have missed any major associations.

Because these data are based on the experience of the first cohorts of women to use oral contraceptives they reflect the long-term risks and benefits for the contraceptives first brought to market. In this cohort, few of these women used oral contraceptives after 1976; thus, the mortality associations reflect use, in large part, of high-dose pills. Formulations have changed, and the doses of estrogen and progesterone have been decreased. The products currently in use contain as little as one fifth the dose of estrogen and one sixth the dose of progestin of the early preparations. As formulations change, risks and benefits may also change. To date, the major documented effect of lower-dose oral contraceptives has been a reduction in the magnitude of risk for cardiovascular diseases (17), although the effect on ovarian or other cancers may vary with dose. In addition to changes in formulation, patterns of use have altered over time. We cannot address long-term use before first pregnancy in this cohort. Accordingly, results may vary among studies because of different patterns of use including total duration of use and different formulations. We note that the mean duration of use was 49 months (median, 35 months) and that 39% used oral contraceptives for less than 2 years (hence the reduction in risk for ovarian and endometrial cancer mortality did not achieve the levels seen in some other studies) (2, 18).

In one of the two previously reported British cohort studies (4), women who had used oral contraceptives were at no increased risk for mortality (relative risk, 0.9; CI, 0.7 to 1.2), whereas in the other study (12) they were at increased risk for death (relative risk, 1.4; CI, 1.1 to 1.8), largely caused by excess cardiovascular mortality (ischemic heart disease and subarachnoid hemorrhage). We have also reported an increase in car-

Table 4. Use of Oral Contraceptives in 1976 and Mortality during the Subsequent 12 Years of Follow-up

Mortality	Current User*	Past User*
Cancer mortality	0.95 (0.72 to 1.26)	0.91 (0.81 to 1.03)
Breast	1.63 (1.07 to 2.49)	1.01 (0.80 to 1.27)
Ovary	0.82 (0.33 to 2.05)	0.79 (0.57 to 1.17)
Uterus	. . .	0.35 (0.10 to 1.21)
Cardiovascular disease mortality	0.99 (0.62 to 1.60)	0.85 (0.70 to 1.04)
Coronary heart disease	0.70 (0.33 to 1.51)	0.80 (0.61 to 1.05)
Stroke	1.45 (0.72 to 2.95)	0.99 (0.68 to 1.42)
Suicide	1.50 (0.71 to 3.14)	1.24 (0.82 to 1.88)

* Relative risk adjusted for age, smoking, body mass index, and follow-up intervals. Ninety-five percent CIs are shown in parentheses.

diovascular disease incidence among women currently using oral contraceptives (19, 20); however, we observed no increase in cardiovascular mortality. Given the relatively small number of deaths in the two previous cohort studies, the confidence intervals from those studies were wide and compatible with the lack of association that we observed for total mortality.

In part, the mortality data we present for breast cancer and cardiovascular disease reflect the associations for incident disease previously reported from this cohort for oral contraceptive use. However, these two end points account for only one third of all mortality during the 12-year follow-up. We reported that current use, but not past use, is associated with an increased incidence of breast cancer (relative risk, 1.53) (16). Among current users, breast cancer was diagnosed at a later stage than among never-users of oral contraceptives. This finding of increased mortality from breast cancer among current users is also consistent with the observed increased incidence reported by Thomas and Noonan from the World Health Organization collaborative study of neoplasia and steroid contraceptives (7). Because the tumors are more advanced among current users, perhaps this reflects the type of breast cancer that is promoted by oral contraceptives. Access to health care is unlikely to account for the delay in diagnosis because women must see a health care provider to renew prescriptions for oral contraceptives.

In this cohort, current use of oral contraceptives was also associated with increased incidence of coronary heart disease (relative risk, 2.2) (19) and decreased incidence of ovarian and endometrial cancers (3, 21). The apparent protection against ischemic heart disease, but not stroke, among ever-users of oral contraceptives compared with never-users suggests that these relations may be mediated through different mechanisms. Specifically, we noted that 9 of the 19 deaths among women dying of cardiovascular causes who had used oral contraceptives for 10 or more years were caused by stroke.

Kay (22) found an increase in risk for suicide based on data from the Royal College of General Practitioners study, whereas Vessey and colleagues (3), examining attempted suicide and suicide mortality, failed to observe an association. We noted a possible increased risk for suicide for ever-users of oral contraceptives, but this association did not reach statistical significance. A somewhat stronger relation was observed for current use; however, the confidence intervals remained broad. It is possible that this finding reflects the higher levels of progestogen used in the oral contraceptives that were

Table 5. Past Duration of Oral Contraceptive Use in 1976 and Relative Risk for Mortality during 12 Years of Follow-up, Nurses' Health Study, 1976–1988

Variable	Duration of Past Use (Months)					
	Never	1 to 12	13 to 23	24 to 59	60 to 119	120+
Total mortality						
Cases, *n*	1906	263	66	207	200	64
Relative risk*	1.0	0.99	0.85	0.97	1.10	1.05
(95% CI)		(0.87 to 1.13)	(0.66 to 1.10)	(0.83 to 1.13)	(0.95 to 1.28)	(0.81 to 1.34)
Relative risk†		0.91	0.75	0.89	1.02	1.06
(95% CI)		(0.80 to 1.04)	(0.59 to 0.96)	(0.77 to 1.04)	(0.88 to 1.19)	(0.83 to 1.35)
Cardiovascular mortality						
Cases, *n*	403	43	8	28	33	19
Relative risk*	1.0	0.83	0.54	0.63	0.94	1.54
(95% CI)		(0.60 to 1.14)	(0.27 to 1.09)	(0.42 to 0.95)	(0.66 to 1.34)	(0.98 to 2.45)
Relative risk†		0.76	0.49	0.68	0.88	1.60
(95% CI)		(0.55 to 1.06)	(0.24 to 0.98)	(0.47 to 0.99)	(0.63 to 1.23)	(1.10 to 2.33)
Cancer mortality						
Cases, *n*	966	137	34	113	101	26
Relative risk*	1.0	1.05	0.93	1.10	1.13	0.84
(95% CI)		(0.87 to 1.26)	(0.65 to 1.32)	(0.89 to 1.35)	(0.91 to 1.39)	(0.07 to 1.24)
Relative risk†		0.93	0.77	1.00	0.99	0.80
(95% CI)		(0.78 to 1.12)	(0.55 to 1.09)	(0.83 to 1.21)	(0.82 to 1.20)	(0.59 to 1.09)

* Age-adjusted relative risk.
† Multivariate relative risk adjusted for age, cigarette smoking, body mass index, and follow-up interval.

marketed through the 1970s and the altered mood that may result from the exogenous progestogen.

Data on mortality reduce the potential for detection bias that may arise from greater access to medical care or more frequent visits to renew prescriptions and may inflate observed associations with incident disease. This mortality analysis avoids the nonfatal morbidity that may be increased, or decreased, among current users of oral contraceptives and may thus be less useful to aid understanding of causative mechanisms. From a public health perspective, however, total mortality provides an unbiased estimate of the effect of use of oral contraceptives.

Although continued follow-up of this and other cohorts may help elucidate any delayed effects of oral contraceptives, such as a potential reduction in risk for breast cancer among older women who used oral contraceptives before their first birth (23, 24), the current data are reassuring to the generation of women who used the first oral contraceptives that were brought to market in that the risks and benefits of use are balanced with regard to their subsequent risk for death.

In comparison with other forms of contraception used in this cohort, oral contraceptives show equivalent long-term safety. Spouses of the participants who used vasectomy as their form of contraception showed no overall increase in mortality even 20 years after the procedure, although there was the suggestion of increased cancer mortality with long-term follow-up (25). In contrast, tubal ligation is associated with decreased risk for ovarian cancer in this and other studies (26). Based on these data, we conclude that use of oral contraceptives is safe. Ever-users may have a slight reduction in total mortality compared with never-users. Such a reduction is the sum of increased risks for some diseases and decreased risks for others. These effects appear to balance. This study provides no evidence that long durations of oral contraceptive use adversely affect long-term risk for mortality.

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References

1. **Committee on the Relationship between Oral Contraceptives and Breast Cancer.** Oral Contraceptives and Breast Cancer. Institute of Medicine. Washington, DC: National Academy Press; 1991:1
2. **Hankinson SE, Colditz GA, Hunter DJ, Spencer TL, Rosner B, Stampfer MJ.** A quantitative assessment of oral contraceptive use and risk of ovarian cancer. Obstet Gynecol. 1992;80:708-14.
3. **Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH, Speizer FE.** A prospective study of exogenous hormones and risk of endometrial cancer [Abstract]. Am J Epidemiol. 1986;124:520.
4. **Vessey MP, Villard-Mackintosh L, McPherson K, Yeates D.** Mortality among oral contraceptive users: 20 year follow up of women in a cohort study. BMJ. 1989;299:1487-91.
5. **Thomas DB.** Oral contraceptives and breast cancer. J Natl Cancer Inst. 1993;85:359-64.
6. **Romieu I, Berlin JA, Colditz G.** Oral contraceptives and breast cancer. Review and meta-analysis. Cancer. 1990;66:2253-63.
7. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Breast cancer and combined oral contraceptives: results from a multinational study. Br J Cancer. 1990;61:110-9.
8. **Tietze C, Lewit S.** Life risks associated with reversible methods of fertility regulation. Int J Gynaecol Obstet. 1978-1979;16:456-9.
9. **Ory HW.** The noncontraceptive health benefits from oral contraceptive use. Fam Plann Perspect. 1982;14:182-4.
10. **Vessey MP.** The Jephcott Lecture, 1989. An overview of the benefits and risks of combined oral contraceptives. In: Mann RD; ed. Oral Contraceptives and Breast Cancer. Park Ridge, New Jersey: Parthenon Press; 1990:1221-32.
11. **Milne R, Vessey M.** The pill and mortality—an overview. J Public Health Med. 1992;14:9-16.
12. Royal College of General Practitioners' Oral Contraceptive Study. Further analyses of mortality in oral contraceptive users. Lancet. 1981;1:541-6.
13. **Colditz GA.** The Nurses' Health Study: findings during 10 years of follow-up of a cohort of US women. Curr Probl Obstet Gynecol Fertil. 1990;13:129-74.
14. **Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al.** Test of the National Death Index. Am J Epidemiol. 1984;114:837-9.
15. **Miettinen OS.** Estimability and estimation in case-referent studies. Am J Epidemiol. 1976;103:226-35.
16. **Romieu I, Willett WC, Colditz GA, Stampfer MJ, Rosner B, Hennekens CH, et al.** Prospective study of oral contraceptives use and the risk of breast cancer in women. J Natl Cancer Inst. 1989;81:1313-21.
17. **Thorogood M, Mann J, Murphy H, Vessey M.** Fatal stroke and use of oral contraceptives: findings from a case-control study. Am J Epidemiol. 1992;136:35-45.
18. **Whittemore AS, Harris R, Itnyre J.** Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Am J Epidemiol. 1992;136:1184-203.
19. **Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH.** A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. N Engl J Med. 1988;319:1313-7.
20. **Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH.** Past use of oral contraceptives and cardiovascular disease: a meta-analysis in the context of the Nurses' Health Study. Am J Obstet Gynecol. 1990;163:285-91.
21. **Colditz GA, Willett WC, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE.** Parity, oral contraceptives, and risk of ovarian cancer [Abstract]. Am J Epidemiol. 1986;124:520.
22. **Kay CR.** The Royal College of General Practitioners Oral Contraceptive Study: some recent observations. Clin Obstet Gynaecol. 1984;11:759-86.
23. **Wingo PA, Lee NC, Ory HW, Beral V, Peterson HB, Rhodes P.** Age-specific differences in the relationship between oral contraceptive use and breast cancer. Cancer. 1993;71:1506-17.
24. **Rosenberg L, Palmer JR, Clarke EA, Shapiro S.** A case-control study of the risk of breast cancer in relation to oral contraceptive use. Am J Epidemiol. 1992;136:1437-44.
25. **Giovannucci E, Tosteson TD, Speizer FE, Vessey MP, Colditz GA.** A long-term study of men who have undergone vasectomy. N Engl J Med. 1992;326:1392-8.
26. **Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Hennekens CH, Speizer FE.** Tubal ligation, hysterectomy, and reduced risk of ovarian cancer: a prospective study. JAMA. 1993;270:2813-8.