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Original article

Oral contraceptives and menopausal hormone therapy: relative and attributable risks of cardiovascular disease, cancer, and other health outcomes

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ABSTRACT

Purpose: To summarize the relative risks (RRs) and attributable risks (ARs) of major health outcomes associated with use of combined oral contraceptives (OCs) and menopausal hormone therapy (HT).
Methods: For OCs, measures of association are from meta-analyses of observational studies. For HT, these measures are from the Women's Health Initiative, a large randomized trial of HT for chronic disease prevention in postmenopausal women aged 50 to 79 years.
Results: Current OC use increases risks of venous thromboembolism and ischemic stroke. However, women of reproductive age are at low baseline risk, so the ARs are small. OC use also increases risk of breast and liver cancer and reduces risk of ovarian, endometrial, and colorectal cancer; the net effect is a modest reduction in total cancer. The Women's Health Initiative results show that HT does not prevent coronary events or overall chronic disease in postmenopausal women as a whole. Subgroup analyses suggest that timing of HT initiation influences the relation between such therapy and coronary risk, and its overall risk-benefit balance, with more favorable effects (on a relative scale) in younger or recently menopausal women than in older women or those further past the menopausal transition. However, even if the RR do not vary by these characteristics, the low absolute baseline risks of younger or recently menopausal women translate into low ARs in this group.
Conclusions: OC and HT can safely be used for contraception and treatment of vasomotor symptoms, respectively, by healthy women at low baseline risk for cardiovascular disease and breast cancer.

Introduction

This article summarizes recent data on the relative risks (RRs) and attributable risks (ARs) of cardiovascular disease (CVD), cancer, and other health outcomes associated with use of oral contraceptives (OCs) and menopausal hormone therapy (HT). RR, which refers to the hazard ratio (HR) in cohort studies or the odds ratio (OR) in case-control studies, is commonly used by epidemiologists to quantify the strength of a relation but falls short in conveying the potential impact of an exposure on an individual person (the usual understanding of risk) to clinicians and patients. AR, also known as the risk difference, is more useful for the latter purpose. The AR percent (AR%), defined as the proportion of disease among the exposed that is attributable to the exposure, is also presented. For OCs, RR, AR, and AR% are derived from observational studies as relevant randomized trials do not exist. For HT, these measures are derived from the Women's Health Initiative (WHI), a large-scale randomized trial.

Oral contraceptives

OCs prevent unwanted pregnancy and confer noncontraceptive benefits, including treatment of menstrual cycle irregularity, heavy menstrual bleeding, premenstrual syndrome, perimenopausal vasomotor symptoms, and acne or hirsutism [1]. In the United States, 82% of sexually experienced women aged 15 to 44 years are current or former OC users [2]. Of the 17% of US women of reproductive age who currently use OCs, nearly all (>99%) take combined OCs (pills containing both estrogen and progestin) [3]; less than 1% use progestin only [4].

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Early observational studies linked combined OCs, which were first marketed in the 1960s, to an increased risk of cardiovascular events [5,6]. However, today's formulations contain much lower hormone doses than did the original pills. Typical estrogen doses in OCs prescribed in the 1960s, 1970s, and 1980s (and beyond) were 100 or more, approximately 50, and 30 μg or less, respectively [7]. Today, about two-thirds of current OC users in the United States take pills containing 30 to less than 50 μg of ethinyl estradiol (low-dose OCs), one-third take pills containing 20 μg (very low–dose OCs), and 2% take high-dose pills containing 50 μg [3]. A greater variety of progestins are also available. In addition, because it is now recognized that OC-associated cardiovascular risks are amplified (on a relative as well as absolute scale) in women with risk factors such as smoking, hypertension, diabetes, and obesity [8], potential candidates for OC use are typically screened for cardiovascular risk before receiving a prescription. Thus, OC users in contemporary studies likely have a better cardiovascular profile than those in earlier eras. A focus on recent data is warranted to assess the health outcomes of contemporary OCs.

Cardiovascular disease

A 2013 meta-analysis of case-control and cohort studies published from 1995 to 2012 found that current versus noncurrent use of contemporary OCs was associated with statistically significant increases in risks of venous thromboembolism (VTE) and ischemic stroke but not hemorrhagic stroke or myocardial infarction (MI) [9] (Table 1). There were insufficient data to calculate OC-associated risks according to age or other cardiovascular risk-factor strata. However, as noted previously, effect modification by these factors is well known—for example, OC-associated risk of VTE are amplified in women with thrombophilia (e.g., factor V Leiden), and OC-associated risks of MI are largely limited to smokers aged 35 years or older [8,10]—and reflected in current prescribing guidelines [11]. Earlier studies have also established that duration of OC use is unrelated to risk among current users and that discontinuation of use leads to a rapid return to the baseline risk of CVD [10,12].

Some studies suggest that combined OCs containing third- (gestodene, desogestrel, norgestimate) or fourth- (drospirenone, dienogest, cytoproterone acetate) generation progestins may increase risk of VTE to a greater degree than combined OCs containing the second-generation progestin levonorgestrel [9,13]. However, prescription bias cannot be ruled out. Women with thrombotic risk factors or who did not tolerate previous formulations may be more likely to be given newer agents. Progestin-only OCs do not raise risks of VTE, ischemic stroke, or MI [9,14,15].

Although combined OCs triple the risk for VTE and double the risk for ischemic stroke in women of reproductive age (and thus account for two-thirds and one-half of VTE and stroke cases among users, respectively [shown by the AR% in Table 1]), these scary-sounding risk elevations should be viewed in the context of the low baseline risk of these events among women in this age group. Estimates of baseline risk vary but are likely close to approximately 4 to 5, 2.4, and 1.3 cases/10,000 woman-years for VTE, ischemic stroke, and MI, respectively [16–18]. Thus, the number of excess VTE events attributable to combined OC use is approximately 10/10,000 woman-years; the corresponding figures for ischemic stroke and MI (if the latter is causal) are 2.4 and 0.4/10,000 woman-years. The likelihood of an individual OC user experiencing a treatment-associated CVD event is acceptably low. In addition, because the VTE risk is as high as 29/10,000 woman-years during pregnancy and 300 to 400/10,000 woman-years shortly after giving birth, OC users are at decreased risk of VTE compared with pregnant and newly parous women [16].

Cancer

Cancer outcomes associated with OC use in very recent meta-analyses are listed in Table 2. Although the focus of this review is on meta-analytic data, relatively recent findings from the Royal College of General Practitioner's Oral Contraception Study, which followed 23,000 users of (mostly) high-dose combined OCs and 23,000 never users (mean age, 29 years) in the United Kingdom for 36 years, are additionally provided (Table 3) to show the AR of various cancers calculated across a uniform follow-up period [19].

Breast cancer

In a 1996 meta-analysis of 54 case-control and cohort studies, ever versus never use of combined OCs was associated with a significant 7% elevation in risk for breast cancer [20]. Current use was associated with a 24% (95% confidence interval 15–33%) elevation that persisted for nearly a decade after discontinuation of treatment (OR for 1–4, 5–9, and ≥10 years after stopping were 1.16 [1.08–1.23], 1.07 [1.02–1.13], and 1.01 [0.96–1.05], respectively). Risk also increased with increasing duration of use, but the trend was not statistically significant. Risk did not vary by estrogen dose. A 2013 meta-analysis of observational studies published between 2000 and 2012 found a similar pattern of results; ever versus never use was associated with an OR of 1.08 (1.00–1.17), with ORs for time since last use of 0–5, 5–10, 10–20, and >20 years of 1.21 (1.04–1.41), 1.17 (0.98–1.38), 1.13 (0.97–1.31), and 1.02 (0.88–1.18), respectively [21]. There was significant heterogeneity in findings across studies. The extent to which differences in characteristics of

Table 1
Cardiovascular disease outcomes associated with current versus noncurrent use* of combined oral contraceptives (OCs) in meta-analyses of observational studies published between 1995 and 2012

CVD outcome	Number of studies	Summary OR (95% CI)	I_e	I_u	AR	AR%
VTE	14	2.97 (2.46–3.59)	15	5	10	67
Ischemic stroke	7	1.90 (1.24–2.91)	4.8	2.4	2.4	50
Hemorrhagic stroke	4	1.03 (0.71–1.49)	—	—	—	—
MI	8	1.34 (0.87–2.08)	1.7	1.3	0.4	23

AR = attributable risk, calculated as I_e-I_u and expressed as number of events per 10,000 person-years; AR% = attributable risk percent, calculated as $100 \times (I_e - I_u)/I_e$; CI = confidence interval; I_e = incidence in exposed group (women currently using OCs), expressed as number of events per 10,000 person-years; I_u = incidence in unexposed group (women not currently using OCs), expressed as number of events per 10,000 person-years; OR = odds ratio.

* Effects on cardiovascular disease outcomes do not persist after discontinuation of use, so comparing current to noncurrent users is the most appropriate global comparison.

ORs are from reference [9]; I_u for VTE is from reference [16]; I_u for ischemic stroke and MI is reference [18]. I_e, AR, and AR% are computed from data provided in source documents.

Table 2
Cancer outcomes associated with ever versus never use* of combined oral contraceptives in meta-analyses of observational studies published between 2000 and 2012

Cancer outcome	Number of studies	Summary OR (95% CI)	Increase or decrease in lifetime absolute risk, %
Breast cancer	23	1.08 (1.00–1.17)	0.89
Ovarian cancer	24	0.73 (0.66–0.81)	−0.54
Endometrial cancer	7	0.57 (0.43–0.77)	−1.77
Colorectal cancer	11	0.86 (0.79–0.95)	−0.76

OR = odds ratio; CI = confidence interval.

* Effects on cancer persist for 10 to 30 years after discontinuation of use, so comparing ever versus never users is an appropriate global comparison.

References [21,23].