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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 (RR) and attributable risks (AR) 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 (WHI), a large randomized trial of HT for chronic disease prevention in postmenopausal women aged 50–79.

Results—Current OC use increases risks of venous thromboembolism and ischemic stroke. However, women of reproductive age are at low baseline risk, so the AR 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 WHI 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, as well as 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.

Conclusion—OC and HT can safely be used for contraception and treatment of vasomotor symptoms, respectively, by healthy women at low baseline risk for CVD and breast cancer.

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Keywords

attributable risk; attributable risk percent; coronary heart disease; cancer; epidemiology; estrogen; hazard ratio; menopausal hormone therapy; mortality; observational studies; oral contraceptives; progestin; randomized clinical trials; relative risk; stroke; venous thromboembolism; women

INTRODUCTION

This article summarizes recent data on the relative risks (RR) and attributable risks (AR) 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 attributable risk 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, 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 U.S., 82% of sexually experienced women aged 15-44 are current or former OC users (2). Of the 17% of U.S. women of reproductive age who currently use OCs, nearly all (>99%) take combined OCs (pills containing both estrogen and progestin) (3); <1% use progestin only (4).

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, ~50, and 30 µg, respectively (7). Today, about two-thirds of current OC users in the U.S. take pills containing 30-~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 1995-2012 found that current vs. 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 above, effect modification by these factors is well known—e.g., 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 (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 ~4-5, 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 ~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 300-400/10,000 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) in the U.K. 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 vs. 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 following discontinuation of treatment (OR for 1-4, 5-9, and 10 years post-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 2000-2012 found a similar pattern of results; ever vs. 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 OC users or preparations account for this heterogeneity is unclear. A 2012 comprehensive review of the literature by the International Agency for Research on Cancer (IARC) concluded that RRs are highest for use prior to first pregnancy or at an early age (22). OCs taken after a first pregnancy may confer less risk because pregnancy stimulates breast cells to differentiate, making them less sensitive to hormonal effects. With respect to ARs (which depend not only on RRs but also the rising baseline risk of breast cancer with age), the 1996 meta-analysis reported that among 10,000 North American or European women who used combined OCs from ages 16-19, 20-24, 25-29, 30-34, 35-39, and 40-44, respectively, the estimated excess number of breast cancers diagnosed up to 10 years after stopping use would be 0.5, 1.5, 4.7, 11.1, 21.0, and 32.0 (20). The 2013 meta-analysis estimated the increase in lifetime absolute risk of breast cancer associated with ever vs. never use of OCs at ~0.89% (21).

Ovarian cancer—The IARC review concluded that OCs reduce ovarian cancer risk and that the risk reduction is greater with increasing duration of use and persists for 30 years after cessation of use (22). In a 2008 meta-analysis of 45 case-control and cohort studies, the proportional risk reductions in ovarian cancer incidence per 5 years of OC use were 29% (23-34%), 19% (14-24%), and 15% (9-21%) for use that had stopped <10, 10-19, and 20-29 years prior (7). Despite falling OC estrogen doses during the 1960s, 1970s, and 1980s, the strength of the risk reductions did not vary across calendar time. An estimated 4 ovarian cancers before age 75 were prevented for every 10,000 woman-years of use in high-income countries (7). A 2013 meta-analysis of observational studies published between 2000-2012 reported an OR of 0.73 (0.66-0.81) for ever vs. never use (23). Compared with never users, women who used OCs for <1, 1-5, 5-10, and >10 years had ORs of 0.91 (0.78-1.07), 0.77 (0.66-0.89), 0.65 (0.55-0.77), and 0.43 (0.37-0.51), respectively, and women who had last used OCs <10, 10-20, 20-30, and >30 years ago had ORs of 0.41 (0.34-0.50), 0.65 (0.56-0.74), 0.92 (0.76-1.12), and 0.79 (0.58-1.12), respectively. The lifetime reduction in ovarian cancer attributable to use of OCs for a mean of 5 years was estimated to be ~0.54% (23). The protective effect, which likely results from lack of ovulation while on therapy, was seen in women with and without a genetic predisposition to ovarian cancer (22, 24).

Endometrial cancer—The IARC review concluded that, in a pattern similar to that for ovarian cancer, OCs reduce endometrial cancer risk and that the risk reduction is greater with increasing duration of use and persists for 20 years after cessation of use (22). A 2013 meta-analysis of observational studies published between 2000-2012 reported an OR of 0.57 (0.43-0.77) and a decrease in absolute risk of ~1.77% for ever vs. never use (21).

Colorectal cancer—The IARC review concluded that OCs may reduce the risk of colorectal cancer (22). Recent meta-analyses report risk reductions of ~15-20% for ever vs. never use (21, 25), with a decrease in absolute risk of ~0.76% (21).

Other cancers—Some studies have found that OCs increase risk for cervical cancer (21). However, observed associations may be due to the fact that sexually active women are more likely to use OCs and also more likely to contract human papilloma viruses (HPV) that cause cervical cancer. OCs increase risk for hepatic adenoma (26) and, in women at low risk for HBV infection, liver cancer (22); small numbers; however, preclude precise effect estimates. There are few data to suggest that OCs affect risk of cancers not mentioned above (22).

Total cancer—Long-term prospective studies, including the Royal College study (Table 3), suggest that OC use confers a net reduction in cancer risk (19, 27).

Other outcomes

The effect of current use of combined OCs on *bone mineral density* varies by age, with reductions, neutral effects, and increases observed in adolescents, adult premenopausal women, and perimenopausal women, respectively (28). The effect of past use of combined OCs on *fracture risk* after menopause is unclear (28-30). Several studies suggest that OC use reduces *total mortality* (31-33). In the Royal College study, the HR for ever vs. never use was 0.88 (0.82-0.93), and the AR was -5.19/10,000 woman-years (31).

Summary

Calculating a single estimate of the overall benefit-risk balance of combined OC use in the reproductive aged population as a whole is difficult because of differences in study designs, exposure definitions, and length of follow-up intervals and also because of the variable timing of salient outcomes. CVD risks occur primarily during active use, whereas cancer effects may not emerge for many years post-stopping. The benefit-risk balance of OCs also depends on the user's individual health profile. However, for women at low baseline risk of CVD and breast cancer, combined OCs are an appropriate method of pregnancy prevention.

MENOPAUSAL HORMONE THERAPY

Menopausal hormone therapy (HT) has long been recognized as the most effective treatment for the vasomotor symptoms that affect many women during the menopausal transition (34). As recently as 15 years ago, HT had also been promoted as a way to prevent many aging-related chronic diseases, including CHD, cognitive impairment, and osteoporosis. The belief that estrogen protected the heart and that women of all ages could benefit was so strong that many clinicians were initiating HT in patients who were 20-30 years past the menopausal transition or at high coronary risk. This practice was unwarranted in the absence of conclusive data from randomized clinical trials on the balance of risks and benefits of HT when used for chronic disease prevention.

Results from the landmark Women's Health Initiative (WHI), first published in 2002 (35), and smaller trials have now established that the risks of HT outweigh the benefits for many

women (34, 36). In response, the prevalence of HT use among US women, which peaked at >40% in 2001, has fallen sharply (37, 38). The WHI results for the total study population and for subgroups defined by age, time since menopause onset, and other characteristics are summarized here. The findings suggest that it may be possible to identify patients most likely to experience a favorable benefit-risk balance while taking HT for an approved indication: treatment of moderate to severe vasomotor symptoms, and, in women at high fracture risk who cannot tolerate other therapies, prevention of osteoporosis (39).

Overview of WHI HT trials

The WHI HT trials included >27,000 healthy postmenopausal women aged 50-79 (mean age, 63). In the estrogen-progestin trial, 16,608 women with an intact uterus were assigned to oral estrogen plus progestin (0.625 mg of conjugated equine estrogens [CEE] plus 2.5 mg of medroxyprogesterone acetate [MPA]) or a placebo daily (35). In the estrogen-alone trial, 10,739 women with hysterectomy were assigned to oral estrogen alone (0.625 mg of CEE) or a placebo daily (40). The study was powered to detect an effect of HT on CHD (nonfatal MI or coronary death) and to assess the benefit-risk balance over a planned duration of 9 years. The estrogen-progestin trial was halted after an average of 5.6 years of treatment because of a significant increase in breast cancer risk and an unfavorable benefit-risk balance in the overall study population (35). The estrogen-alone trial was halted after 7.1 years because of an excess stroke risk not offset by a reduced CHD risk (40). Although both HT regimens lowered osteoporotic fracture risk, they offered no other clear benefit for chronic disease risk reduction. In 2013, WHI investigators published a comprehensive overview of findings (41). Unless noted, the results given here are from (or derived from) the 2013 report.

HT-associated health outcomes in the total WHI study population

Associations between HT and health outcomes in the total WHI study population are shown in Table 4.

Cardiovascular disease—Women assigned to 5.6 years of estrogen-progestin were 18% more likely to develop **CHD** than those assigned to placebo, although this risk elevation was not statistically significant. During the first year of the trial, there was a significant 80% increase in risk, which subsequently diminished (p, trend by time=0.03). Women assigned to 7.1 years of estrogen alone had neither an increase nor decrease in CHD risk. The results were similar for the outcome of **total MI**. Neither HT regimen affected risk of **coronary revascularization**. Women assigned to estrogen-progestin or estrogen alone were about 35% more likely to suffer a **stroke** than those assigned to placebo; an elevation in risk was found for ischemic but not hemorrhagic stroke (42, 43). Assignment to estrogen-progestin was associated with a nearly twofold increase in risk for **pulmonary embolism** and **deep vein thrombosis**, and assignment to estrogen alone led to a 35-50% increase in these risks. Both HT regimens were associated with a significant 10-15% increase in risk of a composite endpoint of **total cardiovascular events** (MI, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, pulmonary embolism, deep vein thrombosis, and cardiovascular death).

In absolute terms, among every 10,000 women assigned to estrogen-progestin for one year, an estimated additional 6 CHD events, 9 strokes, and 21 VTEs would occur. Considering all event types in the composite cardiovascular outcome, there would be 19 excess cardiovascular events. Among every 10,000 women assigned to estrogen alone for one year, there would be 3 fewer CHD events, 11 more strokes, and 11 more VTEs. Considering the composite cardiovascular outcome, there would be 27 excess cardiovascular events. The AR %, or estimated proportion of all cardiovascular events attributable to use of estrogen with or without progestin in women assigned to these therapies, is 11%.

Cancer—Compared with those assigned to placebo, women assigned to estrogen-progestin experienced a significant 24% increase in the risk of *breast cancer*. In contrast, assignment to estrogen alone led to a borderline significant risk reduction of 21%. Reasons for this apparent protective effect are unclear (44). For *colorectal cancer*, a 38% risk reduction was found for estrogen-progestin, but no benefit was seen with estrogen alone. For *endometrial cancer*, a nonsignificant 17% risk reduction was found for estrogen-progestin. (Estrogen taken alone is known to increase endometrial cancer risk and was not given to women with an intact uterus in the WHI.) Neither HT regimen was associated with risk of *total cancer*.

In absolute terms, among every 10,000 women assigned to estrogen-progestin for one year, 9 additional breast cancers, 6 fewer colorectal cancers, and 1 fewer endometrial cancer would occur. Considering all cancer types, there would be 4 excess cancer cases. The AR%, or estimated proportion of all cancers attributable to use of estrogen-progestin in women assigned to this therapies, is 3%. Among every 10,000 women assigned to estrogen alone for one year, there would be 7 fewer breast cancers and 2 more colorectal cancers, and 11 more VTEs. Considering all cancer types, there would be 8 fewer cancers. The estimated proportion of cancers prevented by use of estrogen alone is 7%.

Other outcomes—Both HT regimens were associated with reductions in risk of *hip fracture*, *type 2 diabetes*, and *gallbladder disease*. Estrogen-progestin also increased *ovarian cancer* risk, but the small number of cases precluded a precise effect estimate. Among women aged 65, estrogen-progestin doubled the risk of *probable dementia*, and estrogen alone led to a 47% increase in risk. Neither HT regimen was associated with *all-cause mortality*. To operationalize the risk-benefit balance of HT, WHI investigators computed a *global index* consisting of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (estrogen-progestin only), hip fracture, and mortality. Analysis of the global index indicated that the health risks of estrogen-progestin outweighed its benefits, with a net effect of 20 additional adverse events per 10,000 women-years. In contrast, the health risks of estrogen alone were about equal to its benefits.

Health changes after stopping HT: Many but not all risks and benefits of active use of HT dissipated within 5-7 years after therapy was stopped. For estrogen-progestin, an elevated risk of breast cancer persisted (HR=1.28 [1.11-1.48]) during a cumulative 12-year follow-up (5.6 years of treatment plus 6.8 years of post-intervention observation), but most CVD risks became neutral. A reduction in hip fracture risk persisted (HR=0.81 [0.68-0.97]), and a significant reduction in endometrial cancer risk emerged (HR=0.67 [0.49-0.91]). For estrogen alone, the reduction in breast cancer risk became statistically significant (HR=0.79

[0.65-0.97]) during a cumulative 12-year follow-up (6.8 years of treatment plus 5.1 years of post-intervention observation), and significant differences by age group (described below) persisted for MI and the global index.

HT-associated risks in subgroups defined by age, time since menopause onset, and other characteristics

WHI investigators conducted exploratory analyses to identify subsets of women for which HT may be especially beneficial or harmful. These analyses suggest that age and/or time since menopause onset affect the relation between HT and CHD (Table 5). Although there was no association between estrogen-only therapy and CHD in the overall study population, such therapy was associated with a borderline significant 40% reduction in CHD among women aged 50–59, whereas there was no risk reduction or even a slight increase at older ages (p , trend by age=0.08). For total MI, estrogen alone was associated with a 45% risk reduction (AR, 11 fewer cases/10,000 woman-years) and a nonsignificant 24% risk increase (AR, 14 excess cases/10,000 woman-years) among the youngest and oldest women, respectively (p , trend=0.02). For coronary revascularization, there was a risk reduction in the youngest women (p , trend by age=0.06). Although age did not have these effects in the estrogen-progestin trial, HT-associated CHD risks increased with years since menopause onset (p , trend=0.08), with a significant 52% elevation in risk among women 20 years past menopause onset. For total MI, estrogen-progestin was associated with a nonsignificant 9% reduction in risk among women <10 years past menopause onset, a 16% increase in risk among women 10–19 years past menopause onset, and a two-fold increase in risk among women 20 years past menopause onset (p , trend=0.01). Data from animal experiments, observational studies, and smaller randomized trials also support a potential interaction between HT and age or time since menopause onset on CHD (45). The interaction may arise from underlying differences in the health of the vasculature between younger or recently menopausal women and those who are older or further past the menopausal transition. Initiation of HT at a young age may ameliorate the endothelial dysfunction and slow the progression of early atherosclerosis, whereas later initiation may render already advanced atherosclerotic lesions more susceptible to inflammatory and hemostatic abnormalities (46, 47).

In contrast to the CHD findings, age or time since menopause onset does not appear to influence risk for HT-induced stroke, VTE, breast cancer, or total cancer. For colorectal cancer, estrogen alone increased the risk in women aged 70-79, but there was no risk elevation in younger women (p , trend by age=0.02). For hip fracture, no effect modification by age was observed with either HT regimen, but small numbers precluded precise effect estimates. For diabetes, there was a near-significant risk elevation in women aged 70-79 but nonsignificant risk reductions in younger women in the estrogen-progestin trial (p , trend=0.10). In the estrogen alone trial, HT-associated HRs increased with age for all-cause mortality (p , trend=0.04) and the global index (p , trend=0.02); for all-cause mortality, a similar trend was seen for strata defined by time since menopause onset (HR for <10, 10-19, 20 years were 0.64, 0.97, and 1.15, respectively, p , trend=0.10). Viewing the global index results from an absolute perspective, there were 19 fewer adverse events per 10,000 woman-years in the youngest age group randomized to estrogen alone and 51 more adverse events

per 10,000 woman-years among the oldest group, compared with their counterparts randomized to placebo.

Other user characteristics also appear to modify HT-associated risks (45). The presence of a favorable lipid profile (48) or absence of metabolic syndrome (49) decreases the likelihood of an HT-associated CHD event, and factor V Leiden genotype interacts with HT to augment VTE risk (50). For breast cancer, the protective effect of estrogen therapy was limited to women without prior HT use; those without benign breast disease; those without a first-degree relative with breast cancer; and those with a 5-year Gail risk score <1.75% (51).

It should be noted that the evidence for differential health effects of HT by age and time since menopause onset, as well as other cardiovascular- or cancer-related characteristics, is strong but not yet conclusive. Nonetheless, even if HT-associated HRs do not vary according to these characteristics, the much lower absolute baseline risks of coronary and other events in younger or recently postmenopausal women means that they have much lower ARs of HT compared with their counterparts who are older or further past menopause.

Summary

The WHI provided clear data on the benefits and risks of HT in women aged 60 and ended the practice of initiating HT in these women for the express purpose of CHD prevention. However, the overall findings likely overstate the risks for healthy younger women who begin HT closer to menopause onset. The use of age-specific absolute rather than relative measures of effect may more clearly put the risks into perspective for patients. Although additional research is needed, it may be possible to develop individualized risk prediction models to distinguish more finely women who are likely to experience favorable outcomes with HT from those who are not.

CONCLUSION

For healthy women with low baseline risk of CVD and breast cancer, OC and HT are “not risk-free but safe-enough” (52) approaches for contraception and vasomotor symptom treatment, respectively.

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Table 1

Cardiovascular disease outcomes associated with current vs. noncurrent use^a of combined oral contraceptives (OCs) in meta-analyses of observational studies published between 1995 and 2012

CVD outcome	# Studies	Summary OR (95% CI)	I _e	I _u	AR	AR%
Venous thromboembolism	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)	--	--	--	--
Myocardial infarction	8	1.34 (0.87-2.08)	1.7	1.3	0.4	23%

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

Abbreviations: OR, odds ratio. 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. 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*(I_e-I_u)/I_e.

Sources: ORs are from Peragallo Urrutia R et al., *Obstet Gynecol* 2013;122:380-9; I_u for VTE is from Reid RL et al., *J Fam Plann Reprod Health Care* 2010;36:117-22; I_u for ischemic stroke and MI is from Lidegaard O et al., *N Engl J Med* 2012;366:2257-66. I_e, AR, and AR% are computed from data provided in source documents.

Table 2

Cancer outcomes associated with ever vs. never use^a of combined oral contraceptives in meta-analyses of observational studies published between 2000 and 2012

Cancer outcome	# 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

^aEffects on cancer persist for 10-30 years after discontinuation of use, so comparing ever vs. never users is an appropriate global comparison.

Abbreviations: OR, odds ratio. CI, confidence interval.

Source: Gierisch JM et al. *Cancer Epidemiol Biomarkers Prev* 2013;22:1931-43; Havrilesky LJ et al., *Obstet Gynecol* 2013;122:139-47.

Table 3

Cancer outcomes associated with ever vs. never use of oral contraceptives in the Royal College of General Practitioner's Oral Contraception Study among 46,000 U.K. women (mean age, 29) who were followed for up to 36 years (1968-2004)

Cancer outcome	I _e	I _u	AR	AR%	HR (95% CI)
Breast cancer	12.15	12.42	-0.27	-2.2	0.98 (0.87-1.10)
Ovarian cancer	1.32	2.47	-1.15	-87.1	0.54 (0.40-0.71)
Endometrial cancer	1.13	1.95	-0.82	-72.6	0.58 (0.42-0.79)
Colorectal cancer	2.60	3.61	-1.01	-38.9	0.72 (0.58-0.90)
Total cancer	34.49	39.04	-4.55	-13.2	0.88 (0.83-0.94)

Abbreviations: I_e, incidence in exposed group (ever users), expressed as number of events per 10,000 woman-years. I_u, incidence in unexposed group (never users), expressed as number of events per 10,000 woman-years. AR, attributable risk, calculated as I_e-I_u and expressed as number of events per 10,000 woman-years. AR%, attributable risk percent, calculated as 100*(I_e-I_u)/I_e. HR, hazard ratio. CI, confidence interval.

Source: Hannaford PC et al., *BMJ* 2007;335:651.

Health outcomes in the overall study population in the Women's Health Initiative hormone therapy trials during the intervention phase^a

Table 4

Outcome	Estrogen-progestin trial						Estrogen-alone trial						p
	I _e	I _u	AR	AR%	HR (95% CI)	p	I _e	I _u	AR	AR%	HR (95% CI)		
Cardiovascular disease													
Coronary heart disease ^b	41	35	6	14.6	1.18 (0.95-1.45)	0.13	55	58	-3	-5.5	0.94 (0.78-1.14)	0.53	
Myocardial infarction	35	29	6	17.1	1.24 (0.98-1.56)	0.07	44	45	-1	-2.3	0.97 (0.79-1.21)	0.97	
Coronary revascularization ^c	42	45	-3	7.1	0.95 (0.78-1.16)	0.64	68	67	1	1.5	1.00 (0.83-1.19)	0.96	
Stroke	33	24	9	27.2	1.37 (1.07-1.76)	0.01	45	34	11	24.4	1.35 (1.07-1.70)	0.01	
Pulmonary embolism	18	9	9	50.0	1.98 (1.36-2.87)	<0.001	14	10	4	28.6	1.35 (0.89-2.05)	0.15	
Deep vein thrombosis	25	14	12	48.0	1.87 (1.37-2.54)	<0.001	23	15	7	30.4	1.48 (1.06-2.07)	0.02	
All cardiovascular events ^d	170	152	19	11.2	1.13 (1.02-1.25)	0.02	251	224	27	10.8	1.11 (1.01-1.22)	0.03	
Cancer													
Breast cancer	43	35	9	20.9	1.24 (1.01-1.53)	0.04	28	35	-7	25.0	0.79 (0.61-1.02)	0.07	
Colorectal cancer	10	17	-6	-60.0	0.62 (0.43-0.89)	0.009	17	15	2	11.8	1.15 (0.81-1.64)	0.44	
Endometrial cancer	6	7	-1	-16.7	0.83 (0.49-1.40)	0.49	NA	NA	NA	NA	NA	NA	
All cancer types ^e	127	124	4	3.1	1.02 (0.91-1.15)	0.69	109	117	-8	-7.3	0.93 (0.81-1.07)	0.30	
Other outcomes													
Hip fracture	11	17	-6	-54.5	0.67 (0.47-0.95)	0.03	13	19	-6	-46.2	0.67 (0.46-0.96)	0.03	
All fracture	161	212	-51	-31.7	0.76 (0.69-0.83)	<0.001	153	214	-61	-39.9	0.72 (0.64-0.80)	<0.001	
Diabetes	72	88	-16	-22.2	0.81 (0.70-0.94)	0.005	134	155	-21	-15.7	0.86 (0.76-0.98)	0.02	
Gallbladder disease	131	84	47	35.9	1.57 (1.36-1.80)	<0.001	164	106	58	35.4	1.55 (1.34-1.79)	<0.001	
Probable dementia ^f	46	23	23	50.0	2.01 (1.19-3.42)	0.01	44	29	15	34.1	1.47 (0.85-2.52)	0.17	
All-cause mortality	52	53	-1	1.9	0.97 (0.81-1.16)	0.76	80	77	3	3.7	1.03 (0.88-1.21)	0.68	
Global index ^g	189	168	20	10.6	1.12 (1.02-1.24)	0.02	208	204	4	1.9	1.03 (0.93-1.13)	0.63	

^aMedian length of randomized treatment was 5.6 years for estrogen-progestin and 7.1 years for estrogen alone.^bCoronary heart disease is defined as nonfatal myocardial infarction or coronary death.^cCoronary revascularization is defined as coronary artery bypass grafting or percutaneous coronary intervention.

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^d All cardiovascular events is a composite outcome of MI, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, venous thromboembolism (pulmonary embolism, deep vein thrombosis), and cardiovascular death.

^e All cancer types except for non-melanoma skin cancer.

^f Probable dementia was assessed in women aged 65.

^g Global index=a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (in the estrogen-progestin trial), hip fracture, and mortality.

Abbreviations: I_e, incidence in the exposed group (estrogen-progestin or estrogen alone), expressed as number of events per 10,000 person-years. I_u, incidence in the unexposed group (placebo), expressed as number of events per 10,000 person-years. AR, attributable risk, calculated as I_e - I_u (numbers may not add precisely due to rounding error). AR%, attributable risk percent, calculated as 100*(I_e - I_u)/I_e and computed from data provided in source document. HR, hazard ratio. CI, confidence interval. NA, not applicable due to hysterectomy.

Source: Manson JE et al. *JAMA* 2013;1353-68.

Health outcomes in the Women's Health Initiative hormone therapy trials, according to age at study entry, during the intervention phase^a

Table 5

Outcome	Estrogen-progestin trial						Estrogen-alone trial					
	I _e	I _n	AR	AR%	HR (95% CI)	p	I _e	I _n	AR	AR%	HR (95% CI)	p
Cardiovascular disease												
Coronary heart disease ^b												
50-59 y	23	17	5	21.7	1.34 (0.82-2.19)	0.81	17	28	-11	-64.7	0.60 (0.35-1.04)	0.08
60-69 y	37	37	0	0.0	1.01	(0.73-1.39)	61	63	-3	-4.9	0.95 (0.72-1.24)	
70-79 y	82	63	19	23.2	1.31 (0.93-1.84)		97	90	7	7.2	1.09 (0.80-1.49)	
Myocardial infarction												
50-59 y	19	15	4	21.1	1.32 (0.77-2.25)	0.55	14	25	-11	-78.6	0.55 (0.31-1.00)	0.02
60-69 y	33	31	2	6.1	1.05 (0.74-1.47)		46	48	-2	-4.3	0.95 (0.69-1.30)	
70-79 y	69	47	21	30.4	1.46 (1.00-2.15)		83	69	14	16.9	1.24 (0.88-1.75)	
Coronary revascularization ^c												
50-59 y	20	20	0	0.0	1.03 (0.63-1.68)	0.67	24	41	-17	-70.8	0.56 (0.35-0.88)	0.06
60-69 y	43	52	-9	-20.9	0.85 (0.64-1.13)		79	69	11	13.9	1.13 (0.88-1.46)	
70-79 y	75	70	+5	6.7	1.08 (0.77-1.51)		107	102	5	4.7	1.07 (0.79-1.43)	
Stroke												
50-59 y	15	10	5	33.3	1.51 (0.81-2.82)	0.50	16	17	-1	-6.2	0.99 (0.53-1.85)	0.77
60-69 y	34	23	11	32.4	1.45 (1.00-2.11)		51	33	18	35.3	1.55 (1.10-2.16)	
70-79 y	63	50	13	20.6	1.22 (0.84-1.79)		77	59	17	22.1	1.29 (0.90-1.86)	
Pulmonary embolism												
50-59 y	11	5	6	54.5	2.05 (0.89-4.71)	0.61	10	6	3	30.0	1.53 (0.63-3.75)	0.28
60-69 y	19	11	8	42.1	1.69 (1.01-2.85)		17	10	7	41.2	1.72 (0.94-3.14)	
70-79 y	30	12	18	60.0	2.54 (1.27-5.09)		14	16	-2	-14.3	0.85 (0.39-1.84)	
All cardiovascular events ^d												
50-59 y	82	67	14	17.1	1.19 (0.92-1.53)	0.92	108	123	-16	-14.8	0.84 (0.66-1.06)	0.06
60-69 y	176	161	15	8.5	1.10 (0.94-1.28)		280	236	44	15.7	1.18 (1.03-1.36)	
70-79 y	321	280	41	12.8	1.14 (0.96-1.35)		410	350	60	14.6	1.17 (0.99-1.37)	
Cancer												

Outcome	Estrogen-progestin trial						Estrogen-alone trial					
	I _e	I _u	AR	AR%	HR (95% CI)	p	I _e	I _u	AR	AR%	HR (95% CI)	p
Breast cancer												
50-59 y	33	27	6	18.2	1.21 (0.81-1.80)	0.68	24	29	-5	-20.8	0.82 (0.50-1.34)	0.89
60-69 y	45	38	8	17.8	1.20 (0.89-1.62)		28	39	-10	-35.7	0.73 (0.51-1.07)	
70-79 y	56	41	15	26.8	1.37 (0.90-2.07)		32	27	-5	-15.6	0.86 (0.52-1.43)	
Colorectal cancer												
50-59 y	4	5	-1	-25.0	0.79 (0.29-2.18)	0.66	7	10	-3	-42.9	0.71 (0.30-1.67)	0.02
60-69 y	13	21	-8	-61.5	0.61 (0.37-0.99)		16	19	-2	-12.5	0.88 (0.53-1.47)	
70-79 y	16	28	-11	-68.7	0.58 (0.31-1.08)		33	15	19	57.6	2.24 (1.16-4.30)	
All cancer^e												
50-59 y	83	84	-1	-1.2	0.97 (0.76-1.23)	0.77	71	79	-8	-11.3	0.89 (0.66-1.19)	0.39
60-69 y	142	128	15	10.6	1.11 (0.93-1.31)		114	129	-15	-13.2	0.89 (0.73-1.08)	
70-79 y	171	182	-11	-6.4	0.94 (0.75-1.17)		152	147	6	3.9	1.04 (0.81-1.33)	
Other outcomes												
Hip fracture												
50-59 y	1	3	-3	-300.0	0.17 (0.02-1.45)	0.38	4	1	3	75.0	5.01 (0.59-42.91)	0.33
60-69 y	9	12	-4	-44.4	0.70 (0.38-1.27)		5	12	-6	-120.0	0.47 (0.22-1.04)	
70-79 y	34	48	-14	-41.2	0.71 (0.46-1.12)		39	60	-21	53.8	0.65 (0.42-1.00)	
Diabetes												
50-59 y	74	85	-11	-14.9	0.85 (0.66-1.09)	0.10	131	158	-26	-19.8	0.83 (0.67-1.04)	0.99
60-69 y	61	99	-38	-62.3	0.61 (0.49-0.77)		144	159	-15	-10.4	0.91 (0.76-1.09)	
70-79 y	95	70	+24	25.3	1.35 (0.98-1.88)		119	114	-27	-22.7	0.82 (0.62-1.07)	
All-cause mortality												
50-59 y	21	31	-10	-47.6	0.67 (0.43-1.04)	0.20	29	40	-11	-37.9	0.70 (0.46-1.09)	0.04
60-69 y	51	47	5	9.8	1.07 (0.81-1.41)		78	77	0	0.0	1.01 (0.79-1.29)	
70-79 y	106	102	3	2.8	1.03 (0.78-1.36)		155	129	26	16.8	1.21 (0.95-1.56)	
Global index^f												
50-59 y	103	91	12	11.6	1.12 (0.89-1.40)	>0.99	98	117	-19	-19.4	0.84 (0.66-1.07)	0.02
60-69 y	189	167	22	11.6	1.13 (0.97-1.31)		210	211	-1	-0.5	0.99 (0.85-1.15)	
70-79 y	342	303	38	11.1	1.12 (0.95-1.32)		367	316	51	13.9	1.17 (0.99-1.39)	

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^a Median length of randomized treatment was 5.6 years for estrogen-progestin and 7.1 years for estrogen alone.

^b Coronary heart disease is defined as nonfatal myocardial infarction or coronary death.

^c Coronary revascularization is defined as coronary artery bypass grafting or percutaneous coronary intervention.

^d All cardiovascular events is a composite outcome of MI, stroke, coronary revascularization, angina, heart failure, carotid artery disease, peripheral vascular disease, venous thromboembolism (pulmonary embolism, deep vein thrombosis), and cardiovascular death.

^e All cancer types except for non-melanoma skin cancer.

^f Global index=a composite outcome of coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (in the estrogen-progestin trial), hip fracture, and mortality.

Abbreviations: I_e, incidence in the exposed group (estrogen-progestin or estrogen alone), expressed as number of events per 10,000 person-years. I_u, incidence in the unexposed group (placebo), expressed as number of events per 10,000 person-years. AR, attributable risk, calculated as I_e - I_u (numbers may not add precisely due to rounding error). AR%, attributable risk percent, calculated as 100*(I_e - I_u)/I_e and computed from data provided in source document. HR, hazard ratio. CI, confidence interval.

Source: Manson JE et al. *JAMA* 2013; 310:1353-68.