

Invited Review

Menopause, hormone replacement therapy and cancer

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Abstract

Objective: To comparatively review available evidence on hormone replacement therapy (HRT) and cancer. **Methods:** Qualitative literature review. **Results:** Most potential favorable and adverse effects on cancer risk of HRT are restricted to current users. On the basis of observational epidemiological data, the RR of breast cancer is moderately elevated in current and recent HRT users, and increases by about 2.3% per year with longer duration of use, but the effect drops after cessation and largely, if not totally, disappears after about 5 years. Unopposed estrogen use is strongly related to endometrial cancer risk, but cyclic combined oestrogen–progestin treatment appears to largely or totally reduce this side effect, if progestin are used for at least 14 days per cycle. However, combined HRT may be associated with higher risk of breast cancer as compared to unopposed estrogens. HRT has been inversely related to colorectal cancer, although the issue of causal relation remains open to discussion. No consistent association was reported for ovarian, liver, other digestive or lung cancer. **Conclusions:** Recommendations for prolonged HRT use must be considered on an individual basis, taking into account the presence of other risk factors mainly for breast cancer, such as family history of breast cancer or a personal history of benign breast disease, as well as individual risk for other chronic diseases. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Menopause and age at menopause have a profound effect on the risk of breast and other fe-

male-hormone related cancers, since the slope of incidence for most of these neoplasms levels off around menopause [1].

Age at menopause is a recognized risk factor for breast cancer, with risk increasing with later ages at menopause [2–4]. It is unclear whether latency effects are involved, or whether the association between menopause and breast cancer risk

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varies by different ages at breast cancer diagnosis [4–6]. The most precise and reliable estimate of the influence of age at menopause on breast cancer risk is provided by the collaborative re-analysis of individual data from 51 epidemiological studies of 52 705 women with breast cancer [7], which estimated an increased risk of 2.8% per year of delayed menopause.

Difficulties also exist in understanding and in disentangling the potential effects of type of menopause. Trends similar to those observed for all menopausal types together were detected in women experiencing a surgical menopause in some studies [4,8,9], although the association was weaker in others [6,10]. This is probably attributable to varying definitions of surgical menopause, with some studies including only women with a hysterectomy alone and others also including those with unilateral or bilateral ovariectomy. It has been shown, in fact, that inclusion of women with simple hysterectomy leads to an underestimate on breast cancer risk of the effect of age at menopause, as well as of exogenous hormones [11].

Pooled data from two case-control studies conducted between 1983 and 1994 in Italy [12] on 3576 postmenopausal breast cancers and 3578 controls provided information on the role of age and type of menopause. When all types of menopause were considered together, the floating absolute risks (FARs) [which avoid the definition of an arbitrary reference category [13]] were 0.49 for < 35 years, 0.81 for 35–39 years, 0.82 for 40–44 years, 0.88 for 45–47 years, 1.02 for 48–50 years, 1.23 for 51–53 years and 1.24 for 54–56 years, with a significant linear trend in risk. A stronger association was observed in women reporting a natural menopause, with FARs of 0.14 for women with menopause < 35 years versus 1.20 for those with menopause at 54–56 years (ratio between the two extreme FAR estimates = 8.6). No trend with age at menopause was seen among the overall surgical menopause group, or among groups defined by hysterectomy alone, hysterectomy with unilateral ovariectomy, or bilateral ovariectomy. However, when only women reporting a bilateral ovariectomy were considered, a strong linear trend in risk was observed. No

heterogeneity emerged when risks were evaluated in separate strata of age at diagnosis or interview.

Later menopause has also been associated with increased risks of ovarian [14] and endometrial cancers [15], and perhaps with a reduced risk of colorectal cancer [16], although the issue is still open to discussion.

Of major concern is the effect on cancer risk of hormone replacement therapy (HRT) [17,18]. HRT reduces climacteric symptoms, has favorable effects on bone metabolism and osteoporosis, and possibly on ischemic heart disease and other cardiovascular diseases [19–21]. It may also reduce the risk of colorectal cancer [22]. Total mortality among women who use postmenopausal hormones is lower than among non-users, which to a large extent reflects favorable health characteristics of women who decide to use HRT [23,24].

HRT, however, also has a number of adverse effects, the main ones being a promotional effect on endometrial cancer, and some elevation in the risk of breast and, possibly, ovarian cancers [18,24–26]. These effects on various neoplasms will be considered in the present review.

2. Breast cancer

As with age at menopause, most information on HRT and breast cancer comes from a re-analysis of individual data from 51 epidemiological studies, conducted in 21 countries and including 52 705 women with breast cancer and 108 411 controls [7]. This showed a 2.3% (95% confidence interval, CI, 1.1–3.6%) increase in the relative risk (RR) of breast cancer for each year of HRT use. This corresponds to a RR of 1.35 (95% CI, 1.20–1.49) for current or recent users who had used HRT for 5 years or more, and to a cumulative excess for women who began use of HRT at age 50 of approximately two cases per 1000 women for 5 year users, six cases per 1000 women for 10 year users, and 12 cases per 1000 women for 15 year users. This increase was comparable with the effect on breast cancer of later menopause, since among never users of HRT the RR of breast cancer increased by 2.8% (95% CI, 2.1–3.4%) for each increasing year at menopause. This elevated

risk, however, leveled off after stopping HRT use, and no material excess risk was observed 5 or more years after stopping, as compared to never users.

It is thus clear that the use of HRT for a short time (i.e. < 5 years) to control menopausal symptoms is not related to any material increase in the risk of breast cancer, whereas long-term use increases breast cancer risk in current users [7,27–29]. The biologic mechanism underlying this association remains unclear. Changes in the composition of the breast tissue have been noted following hormone use [30], with greater mammographic densities (an established risk factor for breast cancer). Also of interest is whether genetic factors, including polymorphisms in hormone metabolizing genes, might be etiologically involved. Further research in this area is critically needed.

Another open question is the impact on breast cancer risk of the combination of estrogens and progestins, a therapy effective in reducing the excess endometrial cancer risk associated with estrogen use alone [31]. There are biological reasons to suspect an unfavorable effect of added progestins on breast carcinogenesis, since ovulatory cycles are related to breast cancer risk, and breast mitotic activity is higher during the luteal phase of the cycle (when progesterone levels are at their highest) [32,33]. The role of various estrogens and progestins on cell kinetics [34] and apoptosis [35] remains however, undefined. An early report of a Swedish cohort study [36] suggested that combined HRT may be more strongly related to breast cancer risk than estrogens alone, with a non-significantly elevated relative risk (RR) of 1.2 for ever use of combined therapy and of 4.4 for more than 6 years use, based on 10 cases (hence a wide confidence interval of, 95% CI, 0.9–22.4). An update of the same study [37] confirmed these findings, showing more moderate RRs of 1.4 after 1–6 years and 1.7 after more than 6 years use of combined preparations. The excess risk, moreover, appeared confined to recent users. Three other studies from Britain [38], Denmark [39] and Sweden [40] showed an association between combined HRT and breast cancer. A report from the American Nurses Health Study cohort [41] confirmed some excess breast cancer risk among cur-

rent long-term HRT users: the RRs were 1.3 (95% CI, 1.1–1.5) for conjugated estrogens, 1.3 (95% CI, 1.0–1.7) for other estrogens, and 1.4 (95% CI, 1.2–1.7) for estrogens plus progestins. The most recent study, a case-control study in Sweden involving 3345 women with breast cancer, found a trend of increasing risk with longer duration of different types of combined estrogen–progestin use (RR = 2.4 for women treated for at least 10 years) [42].

A recent report on 46 355 participants followed for a mean of 10.2 years in the Breast Cancer Detection and Demonstration Project showed that women who had used combined estrogen and progestin had a 40% increased incidence rate (RR = 1.4, 95% CI, 1.1–1.8) of developing breast cancer compared with never-users [43]. Furthermore, the risk from combined therapy was greater than that observed with unopposed estrogens (RR = 1.2, 95% CI, 1.0–1.4). The increased risk was limited to use within the prior 4 years; women who had used HRT in the past but stopped use did not have an increased risk for breast cancer. The increased risk was also largely confined to thin women (body mass indices of 24.4 or less), which may reflect the influence of higher average level of endogenous estrogens among heavier women.

Likewise, a population-based case-control study of 1897 postmenopausal cases and 1637 postmenopausal population controls from Los Angeles County [44] found an RR of 1.06 (95% CI, 0.97–1.15) for each 5 years of estrogen replacement therapy use, but of 1.24 (95% CI, 1.07–1.45) for combined estrogen–progestin treatment, thus suggesting that addition of a progestin to HRT enhances the risk of breast cancer relative to estrogen use alone.

The re-analysis of individual data from 51 studies [7], however, found a similar excess breast cancer risk for women using estrogens alone and combined estrogen–progestin treatment, and no marked differences in relation to hormone types or doses of HRT preparations, although information on the compound used was available only for 39% of women, and only 12% used the association with progestins. Furthermore, little information was available about long duration of use of

any specific preparation. The issue, therefore, remains open to discussion and further quantification [45].

A case-control study from Washington state [46] suggested that combined HRT increases the risk of lobular, but not ductal breast carcinoma, but the findings are inconclusive due to the small number of exposed cases.

Another major issue is the time-risk relation after stopping HRT. The effect of steroid hormones is thought to be on the later stages of the process of carcinogenesis (i.e. they are promoters) [47]; consequently, the increased breast cancer risk associated with HRT declines within a few years after stopping use.

Although the absence of a long-term cumulative risk is clearly reassuring, a 20–30% excess risk of breast cancer in women aged 50–65 years — when HRT use is most frequent — has to be weighed against the benefits of HRT on the bone and perhaps on the cardiovascular system, since the incidence of breast cancer in the sixth decade of life is high [24,48–51].

Another open question is whether the relation between HRT and breast cancer risk differs at various ages. Since there are indications that it is influenced by age at diagnosis, with a higher RR in older women [41,52], any risk-benefit ratio is particularly critical and must be carefully and individually assessed for elderly women using HRT after menopause [50,53,54]. However, in the re-analysis of individual data from the 51 studies, no significant interaction was observed between the RR for HRT use and age [7], although elderly women were at a greater absolute risk of breast cancer given increasing incidence trends with age.

There are no data from clinical trials on the HRT–breast cancer association, but the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, which reported increased mammographic density in 3.5% of the estrogen-only group, found this rate to be between 16 and 23% in women receiving different estrogen/progestin schedules [55]. Mammographic parenchymal density has been shown to be a strong predictor of subsequent breast cancer risk [56].

Although HRT has been associated with an increased incidence of breast cancer, use appears

to lead to lower mortality from breast cancer or improved prognosis in some [29,57–60], although not all [23,61], studies. Although some of this effect may be due to increased breast cancer surveillance among hormone users, a favorable biologic effect of hormone use on the characteristics of breast tumors cannot be dismissed [60,62,63].

Although a diagnosis of breast cancer has been conventionally viewed as a contraindication for subsequent HRT use, this notion is being questioned given data showing a favorable effects of HRT on breast cancer prognosis [64]. Although the few studies that have addressed this issue seem to indicate no adverse effects of HRT usage among breast cancer survivors, sample sizes have been limited [65]. Additional studies on this topic are needed [66,67].

In conclusion, the evidence from observational epidemiological studies indicates that the risk of breast cancer is elevated among women using HRT, increases with longer duration of use, is reduced after cessation of use and levels off about 5 years after stopping use.

3. Endometrial cancer

An association of endometrial cancer with menopausal HRT was suggested on the basis of a substantial rise in the incidence of endometrial cancer seen in the United States (particularly in California) in the early 1970s, following widespread HRT use [15]. Two case-control studies, published in 1975 in the same issue of the *New England Journal of Medicine*, confirmed this observation [68,69]. The possibility that this relationship might merely reflect a detection bias in cases was raised, either through increased surveillance of HRT users or estrogens causing bleeding of existing tumors, prompting the diagnosis of endometrial cancer. The presence of more differentiated neoplasms and, hence, better survival rates after cancer diagnosis in HRT users, was also reported [70].

Epidemiological evidence confirmed the association between estrogen use and endometrial cancer, and the persistence of elevated risk several

years after cessation of use [71]. The risk is about two to three times greater in ever than in never users of estrogens, with a summary RR from a meta-analysis of published studies of 2.3 (95% CI, 2.1–2.5; [72]); the risk estimates were similar for cohort (RR 1.7) and case-control studies using hospital (OR 2.2) or population (OR 2.4) controls. The risk was related to duration of use: the RR was 1.4 for use < 1 year, 2.8 for 1–5 years, 5.9 for 5–9 years and 9.5 (95% CI, 7.4–12.3) for ≥ 10 years [72]. The risk was also inversely related with time since last use [72], suggesting that estrogens have a late-stage effect in endometrial carcinogenesis [47,73].

Estrogen-associated risks for endometrial cancer tend to be higher in leaner than overweight women, who have higher available endogenous estrogen levels. The combined effect of exogenous and endogenous estrogens is additive rather than multiplicative, suggesting that exogenous estrogens and obesity act through similar biological mechanisms on the risk of the disease [74]. This suggests either an upper risk threshold and/or some limiting factor (e.g. sex hormone receptors), which stops the estrogen-raising effect of obesity and exogenous estrogen accumulating beyond a certain level [74].

Some studies suggest a greater excess risk of HRT among smokers [75,76], who tend to have lower oestrogen availability, and a lower HRT-related risk among women who had a history of use of combined oral contraceptives [76,77]. Shields and others [78], however, failed to delineate a subgroup that is exempt from the increased risk of endometrial cancer associated with use of unopposed estrogens.

Data on type, dose or regimen or estrogen use are inconsistent, and in general there appears to be no clear association with type of preparation, its potency and bioavailability, dose and duration, although users of high-dose preparations tend to have a higher risk [76,79]. In the meta-analysis by Grady et al. [72], the RR was 3.9 (95% CI, 1.6–9.6) for users of 0.3 mg conjugated estrogens, 3.4 (95% CI, 2.0–5.6) for users of 0.625 mg, and 5.8 (95% CI, 4.5–7.3) for users of ≥ 1.25 mg; it is not clear, however, whether duration and other time factors could be adequately controlled for in

these analyses. As for the type of compound used, the RR was 2.5 for users of conjugated estrogens and 1.3 for users of synthetic estrogens. With reference to pattern or regimen of use, the RR was 3.0 for intermittent and cyclic use and 2.9 for continuous regimens [72]. It is not clear whether differences in the baseline characteristics of women using the various preparations may explain these apparent differences in the RRs.

In terms of population attributable risks, unopposed estrogen treatment has been associated with over 50% of cases of endometrial cancer in North America in the late 1970s [71], and 10–25% of cases in Europe in the 1980s [77,80].

The cyclic addition of progestins to estrogens (for at least 7 days in each treatment cycle) protects against endometrial hyperplasia, which is considered an endometrial cancer precursor, as shown by a multi-center randomized clinical trial [31]. However, data on long-term consequences are not completely reassuring, since, out of 41 patients treated for a mean duration of 8 years, six patients experienced break-through bleeding and two had adenocarcinoma of the endometrium [81].

The summary RR from a meta-analysis [72] of endometrial cancer in women using cyclic combined therapy was 0.8 (95% CI, 0.6–2.2). However, the results from cohort and case-control studies were inconsistent, with the pooled RR being 0.4 for the cohort studies and 1.8 for the case-control studies.

The number of days per month of progestin addition is an important determinant of risk. One study [82] suggested that the RR was reduced from 2.4 to 1.1 for women using progestins for 10 days or more per month. In a population-based case-control study including 832 cases and 1114 controls [83], the RR for ever users was 3.1 for women with fewer than 10 days of added progestins per month and 1.3 (95% CI, 0.8–2.2) for those with 10–21 days of added progestins. Another study on 833 cases and 791 population controls from Los Angeles County [84] showed RRs per 5 years of use of 2.2 for unopposed oestrogen use, 1.9 for estrogens plus progestins for less than 10 days per month, and 1.1 (95% CI, 0.8–1.4) when progestins were given for 10 days or more.

A study conducted in Sweden on 709 cases of endometrial cancer in post-menopausal women and 3368 population controls [85] confirmed a strong association with unopposed estrogens (RR = 6.2 for estradiol and 6.6 for conjugated estrogens for 5 or more years of use). The association was considerably less strong for the combination of estrogens and progestins (RR = 1.6, 95% CI, 1.1–2.4), and the risk was below unity for continuous use of progestins (RR = 0.2, 95% CI, 0.1–0.8 for use lasting 5 years or longer).

Likewise, a record linkage study conducted in Sweden on a cohort of 8438 women at risk of endometrial cancer [37] showed — on the basis of 66 observed cases vs 34.8 expected — a RR of 4.2 (95% CI, 2.5–8.4) for 6 years or more of use of unopposed estrogens, and of 1.4 (95% CI, 0.6–3.3) for combined estrogen and progestin therapy.

In a study of 512 cases of endometrial cancer and 513 population controls conducted between 1994 and 1998 in Ontario, Canada, the RR was 4.1 (95% CI, 2.2–7.7) for use of > 5 years of unopposed HRT, and around 1.5 — of borderline significance — for various types of combined therapies, although numbers of subjects were small in most subgroups [140].

Thus, although the use of estrogens alone may increase endometrial cancer risk, several studies indicate that combined therapy is not related to a major excess of endometrial cancer, if progestins are given for more than 10 or 14 days in each cycle [86].

4. Ovarian cancer

Descriptive studies are consistent with the absence of a major effect of HRT on ovarian carcinogenesis [87]. Major findings of cohort and case-control studies, and re-analyses of individual data on HRT and ovarian cancer risk are shown in Table 1.

Two cohort studies have shown no association between use of HRT and ovarian cancer risk, including the Walnut Creek Study on Contraception [88], based on 16 638 women followed up for 13 years (RR = 1.0), and a Swedish cohort study [89], based on 23 246 women followed up for an

average 8.6 years (RR = 0.99, 95% CI, 0.76–1.27). In contrast, in the American Cancer Society Cancer Prevention Study II [90], based on mortality data of 243 073 women followed up for ≥ 11 years, the RR was 1.71 (95% CI, 1.06–2.77); this elevated risk was not explained by other known or likely risk factors for ovarian cancer.

At least 12 case-control studies (Table 1) and a re-analysis of individual data of 12 U.S. case-control studies have provided data on HRT and ovarian cancer risk. Of these, seven studies from the U.S. [91], a multi-center case-control study from various U.S. areas [92], a population-based case-control investigation from Canada [93], and four European studies, from the UK [94], Greece [95,96] and Italy [97], reported RRs above unity, i.e. between 1.2 and 1.6.

Other case-control studies published since 1980, including three in the U.S. [98–100], one in Italy [101], and two in Australia [102,103], found no clear relation between ever use of HRT and ovarian cancer risk.

The combined analysis of individual data from 12 U.S. case-control studies, based on 2197 white women with invasive epithelial ovarian cancer and 8893 white controls [104], found a pooled multivariate RR of invasive ovarian cancer for ever HRT use of 0.9 (95% CI, 0.7–1.8) in hospital-based, and 1.1 (95% CI, 0.9–1.4) in population-based studies, and no consistent duration–risk relation, after allowance for age, study, parity and oral contraceptive use. The RR was 0.5 (95% CI, 0.2–1.3) for > 15 years use for hospital-based and 1.5 (95% CI, 0.8–3.1) for population-based studies. The overall RR per year of use was 0.98 for hospital-based and 1.02 for population-based studies; neither estimate was significant. The RR for ever HRT use was 1.1 (95% CI, 0.7–1.7) in a re-analysis of original data considering 327 cases of borderline epithelial ovarian cancers [105].

A collaborative re-analysis of four European studies from the UK, Italy and Greece, based on 1470 ovarian cancer and 3271 hospital controls found a RR of 1.71 (95% CI, 1.30–2.25) for ever HRT use, a weak positive association with duration of use, and some indication that the excess relative risk for ovarian cancer declined with time since last use [106]. The overall RR estimate from

Table 1
Selected studies on hormone replacement treatment (HRT) in menopause and ovarian cancer risk, 1980–1997

Reference	Study design	Number of cases (age group)	Relative risks for ever HRT use	Observations
<i>Cohort studies</i>				
[88], USA (47)	Mortality	6	1.0	13 year mortality follow-up of the Walnut Creek study on contraception
[90], USA (48)	Mortality	436	1.2	Direct relationship with duration. The RR was 1.4 for 6–10 years and 1.7 for ≥ 11 years of use
[127], Sweden (49)	Incidence	64	1.0	Cohort of 23 246 women prescribed HRT, followed for an average of 6.7 years
[89], Sweden (50)	Mortality	52	1.0	As above, follow-up for mortality 8.6 years
<i>Case-control studies</i>				
[100], USA (51)	Hospital-based	62 (65–74)	0.9	Non-significant (95% CI, 0.5–1.6)
[91], USA (52)	Population-based	112 (36–55)	1.3	No consistent duration-risk relationship. Stronger association for endometrioid neoplasms
[101], Italy (53)	Hospital-based	161 (19–69)	1.0	Adjusted for age, area of residence and hysterectomy
[95], Greece (54)	Hospital-based	112	1.6	Non-significant
[98], USA (55)	Hospital-based	116 (20–59)	0.9	Borderline ovarian neoplasms. No consistent duration-risk relationship
[92], USA (56)	Hospital-based	377 (18–69)	1.2	Unopposed estrogens only. No association with combined treatment (RR 0.7), or with specific histotypes. Some duration-risk relationship
[94], UK (57)	Hospital-based	158 (<65)	1.5	Non-significant (95% CI, 0.9–2.6). No association with specific histotypes
[96], Greece (58)	Hospital-based	152 (30–64)	1.4	Non-significant (95% CI, 0.4–4.9)
[97], Italy (59)	Hospital-based	953 (23–74)	1.6	Adjusted for major covariates, including oral contraceptive use. 95% CI, 1.2–2.3. Modest duration-risk relationship
[102], Australia (60)	Population-based	824 (18–79)	1.0	Multivariate RR, 95% CI, 0.8–1.3
[93], Ontario, Canada (61)	Population-based	367	1.3	Multivariate RR 2.0 for serous and 2.8 for mucinous for ≥ 4 years of use. No association with mucinous tumours
[99], USA (62)	Hospital-based	491	0.9	Other cancers as controls. No duration-risk relationship
<i>Overviews</i>				
[104], USA (63)	Pooled analysis of 12 U.S. hospital and population-based case-control studies	2197 (all ages)	0.9/1.1	Invasive cancers. No duration-risk relationship
[105], USA (64)	As above	327 (all ages)	0.9/1.1	Borderline ovarian neoplasms. Hospital-based/population-based studies. No duration-risk relationship

a meta-analysis of all published data was 1.15 (95% CI, 1.0–1.3) for ever use, and 1.27 (95% CI, 1.0–1.6) for > 10 years use [107].

It is not clear whether HRT is related to any specific histologic type of ovarian cancer. A Canadian study [93] reported RRs of 1.4 for serous, 1.9 for endometrioid and 0.7 for mucinous tumors, with significant trends in risk with duration of use for serous and endometrioid tumors. Purdie et al. [103], also found an elevated risk of endometrioid and clear cell ovarian cancers associated with unopposed estrogen use (RR = 2.6, 95% CI, 1.3–4.9). Thus, a strong association between HRT and invasive or borderline malignant epithelial ovarian neoplasms can be excluded, although relationships with some histological types may exist. However, it is possible that ovarian cancers in women who had used HRT are more often classified as endometrioid tumors [108].

Very little information is available on the addition of progestins to estrogen preparations, and it suggests no meaningful association. In a cohort of 4544 women, recruited since 1978 from 21 menopause clinics in Britain and followed up to 1988 [58], no association emerged with ovarian cancer risk (RR = 0.63, non-significant). Similarly, in a multi-center case-control study of 377 cases and 2030 controls conducted between 1976 and 1985 in various U.S. areas [92], only 2% of cases and controls had ever used combination HRT, and the multivariate RR was 0.7 (95% CI, 0.2–1.8).

Thus, the evidence on HRT and ovarian cancer is less consistent than that for endometrial and breast cancer, and available data exclude any strong association between HRT and epithelial ovarian cancer, although a moderate positive association remains open to debate. The potential relation between HRT and non-epithelial ovarian neoplasms has not been adequately assessed.

5. Colorectal cancer

Colorectal cancer is the most frequent neoplasm in non-smokers of both sexes combined in western countries [87,109]. Similar incidences in the two sexes are seen for colon cancer, while a male predominance is found for rectal cancer.

Over the last two decades, mortality rates from colorectal cancer in many developed countries have declined in women but less consistently in men [87]. A role of exogenous female hormones (i.e. oral contraceptives, and HRT) on these trends has been postulated [22].

Eight cohort studies (Table 2) reported information on HRT use and colorectal cancer risk, including a total of over 2400 cases. Most studies showed RRs around or below unity. A significant inverse association was found in two cohort investigations, including the largest one focusing on fatal colon cancers (Table 2). Findings from a recent study also suggested that HRT use may improve short-term survival after a diagnosis with colon cancer ([110]).

Of 12 case-control studies (Table 3) for a total of over 5000 cases, five reported 20–40% significant risk reductions among ever users of HRT. Two additional investigations showed moderate, non-significant inverse associations.

Studies showing an inverse association between HRT use and colorectal cancer were among the largest, and the best controlled. The apparent protection tended to be stronger among recent users. Differences in RRs by duration of HRT use and anatomic subsite were not consistent, but the protective effect seemed stronger in most recent publications. Available studies support the possibility of an inverse association between colorectal cancer and HRT, but prevention and surveillance bias cannot be ruled out [111].

Very few studies have enabled separate evaluation of unopposed from opposed estrogens, since all included few subjects exposed only to opposed estrogens. Of three cohort studies and one case-control investigation, two [59,112] suggested an inverse association of opposed estrogens with cancer of the colon, similar to what observed for HRT of any type. Differences in RRs by anatomic subsite were not consistent, but the data for rectal cancer are scantier than for colon cancer.

A meta-analysis of 20 studies of colorectal cancer published up to December 1996 [113] found an overall RR for ever HRT use of 0.85 (95% CI, 0.7–0.9). The protection was greater for current or recent users (RR 0.69, 95% CI, 0.5–0.9) and

Table 2
Cohort studies on hormone replacement therapy (HRT) and colorectal cancer^a

Reference	Country	Population, (follow-up), no. cancer	Relative risk, RR (95% confidence interval) (ever vs. never users)	Duration of use			Duration of use	Recency of use	Adjustment comments
				Colon-rectum	Colon	Rectum			
[141]	California, US	7345 (4 years) 68		1.00 (n.s.)	–	–	No effect (RR for ≥ 8 year use = 1.02, 0.6–1.8)	Not shown	Age
[127] and [59]	Sweden	22 597 (13 years) 233 (62 deaths)	HRT Estriol Opposed HRT Any type	–	0.9 (0.7–1.1) 1.0 (0.8–1.3) 0.6 (0.4–1.0) 0.9 (0.7–1.2)	0.9 (0.7–1.2) 0.8 (0.5–1.2) 0.8 (0.4–1.3) 0.9 (0.7–1.1)	No effect	Not shown	Age RR for colon mortality = 0.6 (0.4–0.9)
[142] and [115]	US Nurses' Health Study	59 002 (14 years) 470	Current users Past users	0.7 (0.5–0.8) 0.8 (0.7–1.1)	0.6 (0.5–0.9) 0.9 (0.7–1.1)	0.7 (0.4–1.1) 0.8 (0.5–1.2)	No effect (RR for ≥ 5 year use = 0.7, 0.5–1.0)	No risk reduction after 5 years of discontinuation (RR = 0.9; 0.8–1.2)	Age, BMI, OC use, cancer family history, diet, alcohol, smoking, and age at menopause
[143] and [144]	Iowa, US	41 837 (6 years) 293	Former users		0.8 (0.6–1.1)	–	Inverse trend (RR = 0.31 for ≤ 5 year use)	No effect	Age, BMI, W/H ratio, alcohol, exercise, and medical history
[116]	US, Cancer Prevention Study II	42 2373 (7 years) 897 deaths	Current users –		0.7 (0.5–1.1) 0.7 (0.6–0.8)	–	Significant trend (RR for > 11 year use = 0.5, 0.4–0.8)	Stronger effect among current users (RR = 0.5, 0.4–0.8)	Age, BMI, parity, menopause, OC, diet, exercise

Table 2 (Continued)

Reference	Country	Population, (follow-up), no. cancer	Relative risk, RR (95% confidence interval) (ever vs. never users)			Duration of use	Recency of use	Adjustment comments
			Colon- rectum	Colon	Rectum			
[145]	Canada	32 973 (14 years) 230	1.0 (0.7–1.5)	1.3 (0.9–1.9)	0.6 (0.3–1.2)	RR = 0.7 (0.2–2.6) for ≥ 5 years	Not shown	Age Linkage study
[146]	US, BCDDP	33 779 (7.7 years)	Unopp. HRT –	1.1 (0.7–1.5)	1.2 (0.72–2.3)	No effect	RR for recent use = 0.78 (0.55–1.1)	Age (but unaltered by education, BMI, parity and OC use)
		313	Opposed HRT Any HRT	1.4 (0.7–2.5)	–			
[147]	US Leisure World Cohort	7701 (14.5 years) 249	0.81 (0.63–1.04)	0.70 ^b (0.45–1.09)	0.52 ^b (0.21–1.31)	RR = 0.75 for ≥ 15 years	0.66 (0.44–0.98)	Age Significant trend with recency of use

^a BCDDP, Breast cancer detection demonstration project; BMI, body mass index; W/H, waist/hip; OC, oral contraceptives.

^b Recent users (≤ 1 year).

Table 3
Case-control studies on hormone replacement therapy (HRT) and colorectal cancer^a

Reference	Country	Case: control (type of controls)	Relative risk, RR (95% confidence interval) (ever vs. never users)			Duration of use	Recency of use	Adjustment comments	
			Colon-rectum	Colon	Rectum				
[148]	Washington, US	143:707 (population)	≤ 5 years: 1.1 (0.7–1.9) ≥ 6 years: 1.0 (0.6–1.6)	–	–	No trend	Not shown	Age	
[149]	Adelaide, Australia	155:311 (population)	–	0.8 (0.4–1.5)	1.5 (0.8–3.0)	–	–	Reproductive variables (diet was unimportant)	
[150]	Canada	720:349 (cancer patients)	Current users Former users	1.5 (0.8–2.7) 1.1 (0.7–1.9)	–	–	Not shown	Not shown	Age and parity. No distinction was possible between HRT and OC use
[151]	Chicago, US	90:208 (spouses)		0.5 (0.3–0.9)	–	0.2 (0.0–0.8)	No trend	Not shown	Age, parity, hysterectomy
[16,152, 114,125]	Italy	1536:3110 (hospital)		0.6 (0.4–0.8)	0.6 (0.5–0.9)	0.5 (0.3–0.7)	Significant (RR for ≥ 2 year use = 0.5, 0.3–0.8)	RR for ≥ 10 years since last use: 0.5 (0.3–1.0)	Age, education, cancer family history, BMI, parity menopause, OC, and energy intake
[153]	Los Angeles, US	327:327 (neighbours)		< 5 year 5–14 years ≥ 15 years	1.3 (0.9–2.0) 1.1 (0.6–1.8) 1.1 (0.6–1.9)	–	No effect	Not shown	Cancer family history, parity, menopause, exercise, fat, alcohol, and calcium intake
[154]	North America and China	189:494 (neighbours)	North America		2.1 (P = 0.14)	0.5 (P = 0.23)	Not shown. Mostly short duration use	Not shown	Unadjusted (but unaltered by exercise, saturated fat intake and years in the U.S.)
		206:618 (neighbours)	China	2.9		(P = 0.01)	P = 0.56		Artificial menopause was a risk factor in China

Table 3 (Continued)

Reference	Country	Case: control (type of controls)	Relative risk, RR (95% confidence interval) (ever vs. never users)			Duration of use	Recency of use	Adjustment comments
			Colon- rectum	Colon	Rectum			
[155]	Sweden	299:276 (population)	–	0.6 (0.4–1.0)	0.7 (0.4–1.3)	No trend	Not shown	Age. Hormone use included both HRT and OC, but mostly HRT
[122]	Seattle, US	148:138 (population)	–	0.6 (0.4–1.0)	–	Significant trend (RR ≥ 5 year use = 0.5, 0.2–0.9)	RR in current users = 0.5, 0.3–1.0	Age, vitamin intake and hysterectomy. Greater protection in multiparous women
[112]	Wisconsin, US	694:1622 (population)	Unopposed HRT Opposed HRT Any HRT	0.5 (0.3–0.9) 0.5 (0.3–1.1) 0.7 (0.6–0.9)	0.90 (0.46–1.76) 1.1 (0.5–2.5) 1.2 (0.8–1.6)	Significant trend (<i>P</i> = 0.002)	Lower RR for < 10 years since last use = 0.5, (0.4–0.8) for colon	Age, alcohol, BMI, cancer family history, and sigmoidoscopy
[156]	US, KPMC	815:1019 (KPMC members)	–	0.8 (0.7–1.0)	–	No trend (RR ≥ 10 years use = 0.86)	RR for recent use = 0.71, (0.56–0.89)	Age, cancer family history, aspirin and energy intake, OC and exercise
[157]	Detroit, US	60:143 (HMO members)	Current use Past use	0.3 (0.1–1.0) 0.4 (0.1–1.4)	–	Not shown	Not shown	Age, race, reproductive variables, dietary habits, and colonoscopy

^a BMI, body mass index; HMO, health maintenance organization; KPMC, Kaiser Permanente Medical Care; OC, oral contraceptives.

users of more than 5 years (RR 0.73, 95% CI, 0.5–1.0).

The inverse relation between colorectal cancer risk and HRT tends to emerge soon after first exposure [114,115] and seems to level off 5–10 years after cessation. The apparent protection increases with duration in some [112,114] but not all [115,116] studies. Such a pattern seems compatible with the possibility that HRT acts as a promoting agent [47]. Of the few studies on precursors for colorectal cancer, a large prospective investigation [115] found a decreased risk for large colorectal adenomas, but no association for small adenomas. Of concern is the possibility that women may discontinue HRT when symptoms of a disease develop [117], leaving mostly healthy women in the category of current users. However, no difference in risk was found between current users and recent users (i.e. those who had stopped HRT in the past 5 years) [115].

It is, however, important to note that HRT users may differ from non-users in ways that particularly influence colorectal cancer risk (i.e. prevention bias) [118]. Postmenopausal women treated with HRT tend to be of higher social class and more educated [54,118,119]. This selection may imply a healthier lifestyle (e.g. more frequent consumption of vegetables, higher levels of physical activity, and lower prevalence of overweight). In addition, long-term HRT users are, by definition, compliant, which is, per se, a favorable health indicator [118].

Sex hormones modify hepatic cholesterol production and alter bile acid concentration [120]. Secondary bile acids are believed to favor malignant changes in the colonic epithelium. Exogenous estrogens, which decrease secondary bile acid production and can alter intestinal microflora, could, therefore, protect against colorectal cancer. Issa et al. [121] suggested that methylation-associated inactivation of the estrogen receptor (ER) gene in ageing colorectal mucosa could predispose to colorectal tumorigenesis. Exogenous estrogens may thus counteract the natural decline of circulating estrogens in postmenopausal women. However, data on reproductive and menstrual correlates of colorectal cancer risk are inconclusive. Moderate

inverse associations with parity and oral contraceptive use have been reported, but a favorable role of later age at menopause is still unclear [16,122–125].

Additional research is needed to confirm a potentially favorable effect of HRT on colorectal cancer. In western countries, the number of deaths from colorectal and breast cancers in women aged 55 or older are similar (27 000 and 34 000, respectively, in 1994 in the United States, [126]). Thus, a decrease in incidence or mortality from colorectal cancer could greatly affect the balance of risks and benefits associated with the use of HRT.

6. Other neoplasms

A cohort study in Sweden of 23 244 women followed for 6.7 years suggested a moderate excess risk of lung cancer associated with use of estrogens (RR = 1.3, 95% CI, 0.9–1.7; [127]). No information was available on duration of use or any other risk factors. Two case-control studies in the U.S. have also examined the relation of HRT use to risk of adenocarcinomas of the lung. One study, which focused on 181 cases, found a 70% excess risk associated with estrogen replacement therapy, with the RR increasing two-fold for users of 25 or more months usage [128]. Residual confounding by smoking remains, however, possible and in another case-control study, which included 336 cases, no substantial relation was found between HRT use and risk [129].

In the Swedish cohort study mentioned above [127] a total of 13 cases of biliary tract and liver cancers were observed versus 39.7 expected, corresponding to a RR of 0.4 (95% CI, 0.2–0.7). In an Italian case-control study, based on 82 histologically confirmed cases of primary liver cancer and 368 controls, a decrease in risk associated with HRT, though non-significant, was also noted (RR = 0.2, 95% CI, 0.03–1.5) [130]. However, no association between conjugated estrogen and other estrogen use and hepatocellular carcinoma was observed in another case-control study involving 74 cases and 162 population controls from Los Angeles County [131]: the RR was 1.1

for ever use, and 1.0 for > 5 years use. These data are not consistent with an adverse effect of HRT on hepatocellular carcinoma.

Data of HRT and other cancers, including stomach, pancreas and skin melanoma, are limited and inconsistent [18]. A suggestion of an inverse relation between HRT use and squamous cell cervical cancer [132,133] requires further confirmation. In a multicentric U.S. study, HRT was directly associated with adenocarcinoma (OR = 2.1, 95% CI, 0.95–4.6), but weakly inversely related to squamous cell cancer (RR = 0.85, [133]).

7. Other therapeutic approaches

Given the recognized adverse effects of HRT, much recent attention has focused on assessing alternative approaches to treating the menopause, including use of tamoxifen and other selective estrogen receptor modulators (SERMs). These agents are recognized anti-estrogens, which presumably will offer many of the same advantages as HRT, while eliminating some of the disadvantages (no increase in the risk of breast cancer). In fact, the available data seem to indicate that these agents offer substantial advantages in terms of reducing the risk of breast cancer.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP), a total of 13 388 U.S. women who were 60 years of age or older, or who had a 5-year risk of 1.66% or more of developing breast cancer, or who had a history of lobular carcinoma in situ were randomly assigned to receive 20 mg daily of tamoxifen or placebo for 5 years [134]. After 69 months of follow-up, women receiving tamoxifen had a 49% lower risk of invasive breast cancer than placebo-treated women. This beneficial effect of tamoxifen applied to women of all ages, and was particularly evident in women with a history of lobular carcinoma in situ or atypical hyperplasia. The reduction in risk was limited to estrogen receptor (ER) positive tumors. Some adverse effects of tamoxifen, however, were noted in the trial, including excess risks of endometrial cancer, stroke, pulmonary embolism and deep-vein thrombosis, events that oc-

curred more frequently in women aged 50 years or older.

Two other clinical trials of tamoxifen in breast cancer prevention have presented interim results. In a British trial, 2494 women aged 30–70 years with a family history of breast cancer were randomly assigned to tamoxifen or placebo, and followed for up to 8 years [135]. The risk of invasive or in situ breast cancer was 1.06 in the group given tamoxifen compared to the group given placebo. One difference between this and the U.S. trial study was that the British women were allowed to use HRT during the trial (about one-third of study participants were users). In a trial conducted in Italy, 5408 women who had had a hysterectomy were randomized to 5 years of tamoxifen or placebo [136]. The study was stopped early because of patient drop-outs. After a median of 46 months follow-up, there was no difference in breast cancer incidence by treatment arm. Despite the inconsistent trial results, the U.S. FDA has approved use of tamoxifen for breast cancer risk reduction in high risk women [137].

Less information is available on other SERMs. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial of 7705 postmenopausal osteoporotic women under age 81, 60 or 120 mg of raloxifene daily decreased breast cancer risk by 76% (RR = 0.24, 95% CI, 0.1–0.4) as compared to non-users [138]. The protection was stronger for ER positive tumours. Risk for thromboembolic disease was increased three-fold, but there was no increased risk for endometrial cancer in raloxifene-treated compared with placebo-treated women. The U.S. National Cancer Institute and the NSABP Breast Cancer Prevention Trial are now conducting a large, multi-center study to test tamoxifen vs. raloxifene, to determine if raloxifene shows the same risk reduction as tamoxifen, and to determine if the risk for adverse events differs.

Research is also beginning to focus on whether more natural approaches to treating the menopause should be recommended. Although there is growing enthusiasm for use of phytoestrogens, termed by some as *natural* SERMs [139], their effects on cancer risk remain unresolved.

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