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1. Directors of Pharmacy
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Dear Healthcare Professional,

HORMONE REPLACEMENT THERAPY (HRT): FURTHER INFORMATION ON THE KNOWN INCREASED RISK OF BREAST CANCER WITH HRT AND ITS PERSISTENCE AFTER STOPPING

Please see the attached letter from Dr Raine, MHRA providing information about the outcome of the study published in Lancet which identified an increased risk of breast cancer during use of all types of HRT, except vaginal estrogens, and the risk of breast cancer persisting for longer than previously thought after stopping HRT. I would be grateful if you could cascade this information to all relevant colleagues.

Could all Directors of Pharmacy please forward this alert to:-

- Community Pharmacists
- Hospital Pharmacists
- Primary Care Pharmacists

Please could Medical Directors forward this alert to:-

- General Practitioners
- Accident & Emergency Departments
- Directors of Public Health
- Relevant Clinics
- Chief Executives of NHS Board

Thank you for your co-operation.

Yours sincerely

IRENE FAZAKERLEY
Medicines Policy Team

Medicines & Healthcare products Regulatory Agency

MHRA

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Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping

The risk of breast cancer is increased during use of all types of HRT, except vaginal estrogens, and some excess risk of breast cancer persists for longer than previously thought after stopping HRT

Actions for prescribers

- Inform women who use HRT or are considering starting HRT of new information on the risk of breast cancer at their next routine appointment (see patient resources in the Drug Safety Update)
- Only prescribe HRT for relief of menopause symptoms that adversely affect quality of life, and regularly review patients to ensure HRT is used for the shortest time at the lowest dose
- Remind current and past HRT users to be vigilant for signs of breast cancer and encourage them to attend for breast screening when invited

An important new study[1] has confirmed and extended knowledge on the risk of breast cancer with use of systemic HRT (oral or applied under or to the skin as gels or patches [transdermal]).

The risk of breast cancer falls after stopping HRT, but the new analysis shows some excess risk of breast cancer persists for more than 10 years after stopping HRT. This means the total number of additional HRT-related cases diagnosed in the period after stopping HRT up to age 69 years is higher than previously thought. Table 1 provides updated data for total risk of breast cancer, as well as information about other key risks and benefits of HRT for prescribers.

Other key study findings are:

- All types of systemic HRT are associated with a significant excess incidence of breast cancer, irrespective of the type of estrogen or progestogen or route (oral or transdermal)
- There is little or no increase in risk of breast cancer with current or previous use of HRT for less than 1 year; however, there is an increased risk with HRT use for longer than 1 year
- Risk of breast cancer increases further with longer durations of HRT use
- Risk of breast cancer is higher for combined estrogen-progestogen HRT than estrogen-only HRT
- For women who use HRT for similar durations, the total number of HRT-related breast cancers by age 69 years is similar whether HRT is started in her 40s or in her 50s
- The study found no evidence of an effect on breast cancer risk with use of low doses of estrogen applied directly via the vagina to treat local symptoms

What can an individual woman do to reduce her risk?

- Using HRT for as short a time as possible will help to reduce the overall risk
- There are no medical risks with stopping HRT, but symptoms may return especially if HRT is stopped suddenly. Gradually stopping treatment may help to reduce the chances of this
- Low-dose vaginal estrogens do not appear to increase breast cancer risk for women in whom this is a therapeutic option

1. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *The Lancet*. Published August 29, 2019.

Study providing new information on breast cancer risk

The latest evidence comes from a meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer, published 29 August 2019 in The Lancet.[1]

The study confirms previous findings on the risk of breast cancer with systemic HRT and extends knowledge on: persistence of some excess risk (through long-term follow-up of women who stopped using HRT, mostly in the early 2000s), on the breast cancer risks for women who have menopause in their 40s, and on the lack of breast cancer risk in women who use local vaginal estrogen products.

The analysis included 108,647 cases of breast cancer in prospective studies (substantially more cases than the Women's Health Initiative and other randomised trials of HRT) and considered all main types of HRT. Among women with complete follow-up information, mean HRT duration was 10 years in current users and 7 years in past users.

The risk of breast cancer for women who use estrogen-only HRT is lower than the risk with combined HRT, however progestogen is recommended to be added for women with an intact uterus due to the risk of endometrial hyperplasia and cancer with estrogen-only therapy.

The risk of breast cancer for women who use estrogen plus sequential progestogen is lower than with estrogen plus daily progestogen (continuous HRT). However, risks are unaffected by the type of estrogen or progestogen, including progesterone itself, or whether HRT is administered via oral or transdermal routes.

In women who start HRT in their 40s, the total number of HRT-related breast cancers diagnosed by age 69 years is similar to that in women who start HRT in their 50s if HRT is used for a similar duration. It is not known if the risks are similar for women who take HRT following a premature menopause (below age 40), or how their risk may be affected by any underlying conditions.

Estimates of number of extra cases of breast cancer for 5 years HRT use starting around menopause

In the UK around 1 in 16 (about 63 per 1000) women who have never used HRT will be diagnosed with breast cancer between the ages of 50 and 69 years. Among women of average weight who use systemic HRT from menopause in their 40s or 50s, and continue for 5 years, the extra number of cases of breast cancer by age 69 are estimated from the study to be:

- around 1 extra case per 200 women (corresponding to about 5 per 1000) who use estrogen-only HRT
- around 1 extra case per 70 women (corresponding to about 14 per 1000) who used estrogen combined with progestogen for part of each month (sequential HRT)
- around 1 extra case per 50 women (corresponding to about 20 per 1000) who used estrogen combined with daily progestogen HRT (continuous HRT)

The number of extra cases up to age 69 years is approximately double these values for women who use systemic HRT for 10 years compared with those who use HRT for 5 years. A summary of the numbers of HRT-related breast cancers estimated from the new study,[1] plus a summary other risks and benefit for fracture risk with HRT, are provided in table 1.

Prescribers are reminded that HRT should only be initiated for relief of postmenopausal symptoms that adversely affect quality of life and should only be continued as long as the benefit in alleviating symptoms outweighs the risks associated with treatment. In all cases, a careful appraisal of all the risks and benefits (see associated Drug Safety Update article for further data) should be undertaken before use and regularly during use, as a woman's need for treatment and chance of adverse effects changes over time.



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Table 1: Summary of HRT risks and benefits* during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT

	Risks over 5 years use (with no use or 5 years current HRT use)		**Total risks up to age 69** (after no use or after 5 years HRT use†)			**Risks over 10 years** (with no use or 10 years current HRT use)		**Total risks up to age 69** (after no use or after 10 years HRT use†)	
	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**		Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**	Cases per 1000 women with no HRT use	**Extra cases per 1000 women using HRT**
Risks associated with **combined estrogen-progestogen HRT**									
Breast cancer	13	**+8**	63	**+17**		27	**+20**	63	**+34**
Sequential HRT	13	**+7**	63	**+14**		27	**+17**	63	**+29**
Continuous combined HRT	13	**+10**	63	**+20**		27	**+25**	63	**+40**
Endometrial cancer	2	-	10	-		4	-	10	-
Ovarian cancer	2	**+ <1**	10	**+ <1**		4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+7**	26	**+7**		8	**+13**	26	**+13**
Stroke	4	**+1**	26	**+1**		8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-		28	-	88	-
Fracture of femur	1.5	-	12	-		1	-	12	-
Risks associated with **estrogen-only HRT**									
Breast cancer	13	**+3**	63	**+5**		27	**+7**	63	**+11**
Endometrial cancer	2	**+4**	10	**+4**		4	**+32**	10	**+32**
Ovarian cancer	2	**+ <1**	10	**+ <1**		4	**+1**	10	**+1**
Venous thromboembolism (VTE)§	5	**+2**	26	**+2**		10	**+3**	26	**+3**
Stroke	4	**+1**	26	**+1**		8	**+2**	26	**+2**
Coronary heart disease (CHD)	14	-	88	-		28	-	88	-
Fracture of femur	0.5	-	12	-		1	-	12	-

*Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT. †Best estimates based on relative risks of HRT use from age 50 (see DSU table 2 for relative risks). For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use. §Latest evidence suggests that transdermal HRT products have a lower risk of VTE than oral preparations.