

HRT

**AN OVERVIEW OF THE RISKS OF
HORMONE REPLACEMENT THERAPY**

LLOYD'S EMERGING RISKS TEAM REPORT

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EMERGING RISKS TEAM

The Emerging Risks team is part of the Franchise Performance Directorate at Lloyd's. We define an emerging risk as an issue that is perceived to be potentially significant, but which may not be fully understood or allowed for in insurance terms and conditions, pricing, reserving or capital setting. Our objective is to ensure that the Lloyd's market is aware of potentially significant emerging risks so that it can decide on an appropriate response to them.

The Lloyd's Emerging Risks team maintains a database of emerging risks that is updated regularly through conversations with the Lloyd's emerging risks Special Interests Group, which consists of experts within the Lloyd's market put together with help from the Lloyd's Market Association. The team also maintains contact with the academic community, the wider business community and government. Contact with academics is often facilitated through the Lighthill Risk Network, an organisation that is run as not-for-profit funded by Benfield, Catlin, Guy Carpenter and Lloyd's.

More details can be found at <http://www.lloyds.com/emergingrisks>.

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PURPOSE

Hormone replacement therapy (HRT) is used by a large proportion of women over 50 to relieve the symptoms of the menopause. For the insurance industry the principle concern revolves around the potential for class actions by HRT users against HRT manufacturers and the associated potential for liability under General and Product Liability policies.

When HRT emerged in the 1940's it was used as an effective method to combat the sometimes debilitating symptoms of the menopause that typically affect women aged 50 and over. In the 1960's popularity of HRT as a treatment boomed and was claimed to additionally reduce the risk of many other diseases. It appeared that manufacturers had developed a wonder drug for women. However, over time concerns and evidence came to light indicating that the perceived benefits either did not exist or that HRT increased the risk of certain diseases.

While there are several related drugs that are similar to HRT, such as the contraceptive pill, this report will limit its focus to the examination of the risks associated with HRT and possible impact to the insurance industry.

November 2008

EXECUTIVE SUMMARY

1. HORMONE REPLACEMENT THERAPY (HRT) IS

WIDELY USED One in two women participating in the UK's Million Women Study have tried it, and one in three are current users. Examining levels of exposure is the first step for insurers who wish to assess the potential impact of HRT related claims.

2. UNDERSTANDING THE RISK The medical profession and society now have a much greater understanding of the risks involved with HRT, compared to 10 or 20 years ago, thanks to large studies such as the Women's Health Initiative and the Million Women Study. Advice to patients is more consistent and risk-based and it is looking likely that the current legal issues could have a finite lifetime provided that regulatory guidelines are followed.

3. SOME RISKS INCREASE OTHERS REDUCE The overall risk to benefit balance of HRT when prescribed specifically for disease prevention is now considered by US and UK regulators as unfavourable. However, the balance can be favourable for the treatment of symptoms of the menopause. There is an increase in the risk of breast cancer and stroke, and a decrease in the risk of developing colorectal cancer or symptoms of osteoporosis. Heart disease risk may either increase or decrease depending upon the risk factors of each patient.

4. INSURANCE IMPACTS UNCERTAIN If product information is proved to be misleading then product liability could arise. General liability policies may be triggered if Medical Monitoring claims are successful though this type of claim is largely untested against pharmaceuticals. Medical Malpractice may be a target though there is little legal activity in this area.

5. LEGAL UNCERTAINTY Several recent test cases against HRT manufacturers in the US have resulted in awards of significant punitive damages, but many have been later overturned by appeal courts. There is still no definitive answer to whether HRT manufacturers will be found ultimately liable for the risks of HRT. Concerned insurers should follow any legal activity closely as there are thousands of pending cases that will rely upon the rulings of the current test cases.

6. STATISTICAL SIGNIFICANCE The term statistical significance in many scientific papers has been used to indicate the relevance of their findings. However, the method to determine whether a risk has been shown to have increased or decreased depends upon the choice of confidence level, typically 95%. For risk tracking purposes insurers may not wish to exclude risks labelled as "not significant", particularly if the test is only marginally failed.

INTRODUCTION TO HRT

Hormone replacement therapy (HRT) is used primarily as a medical treatment for post-menopause symptoms. The treatment replaces hormones that the body can no longer produce on its own due to age, damage or premature failure of reproductive organs. Treatment is predominately given to women, though HRT for males is also available. The goal of HRT in either sex is to maintain quality of life, as this can be severely affected for some. The table below outlines the hormones used in HRT

Hormones used in HRT

Hormone	Use
Oestrogen	Alleviates: Hot flushes; vaginal dryness; loss of sex drive; depression; incontinence; night sweats; thinning of bone; back and joint pain
Progesterone	Reduces risk of endometrial cancer
Testosterone	Combats loss of sex drive or energy

Source: NHS Direct, The Daisy Network, MHRA

ONE IN TWO WOMEN HAVE TRIED HRT, AND ONE THIRD OF WOMEN AGED 50 TO 64 ARE CURRENTLY USING HRT

There are scores of HRT products on the market but the majority are prepared as either a combination of oestrogen and progesterone or oestrogen alone. The addition of progesterone is to counter the increased risk of endometrial cancer (cancer of the womb lining) that oestrogen induces. If a woman has undergone a hysterectomy then progesterone is not necessary, as the womb lining is not present. In this case the oestrogen only preparation is typically prescribed. Testosterone therapy is also available for combating reduced sex drive.

Many drugs have side effects and HRT is no exception; however, there are several reasons why we believe it is worthy of specific study:

Lack of information in the past regarding hazard/benefit balance

Early observational studies implied that HRT reduced the probability of developing certain diseases. It now appears that the conclusions from these studies were flawed in that the sample of women studied had a lower chance of developing these diseases than national averages. More recent clinical studies have clarified the risks in many areas and now give the opposite view for many diseases after taking into account social, usage and other factors.

Scale of use

A large number of women use HRT. The Million Women Study showed that of the women participating one in two women have tried HRT, and that one third of women aged 50 to 64 are currently using HRT. According to the Office of National Statistics there are about 5.6 million women in the UK in this age bracket. Extrapolating gives 1.9 million women current users. This number can be considered an underestimate of the total number using HRT as a proportion of women aged 65 and above will also be users. The largest geographical markets are the USA, France, Germany, Italy, Spain, UK and Japan.

Legal challenges

Several legal actions have been taken against pharmaceutical companies. Compensatory and punitive damages have been awarded, though many are in appeal. The current trend is for the plaintiff (those seeking compensation) to argue that taking HRT resulted in their developing breast cancer later in life. They also claim to have been misled by advertising stating benefits that later turned out to be false.

Counter arguments for the defendant are typically that they included adequate information about the risks associated with the drug and complied with regulatory requirements. In addition, arguments centre on the difficulty in making a causal link between HRT and developing cancer as there are many other risk factors at play.

Causation

Legal cases to date have highlighted that it is challenging to prove that HRT was the leading cause for developing breast cancer when so many other factors contribute to cancer risk, such as genetic susceptibility, sun exposure and smoking.

Another key issue is whether manufacturers have been misleading with regards to their promotional material, or were simply reflecting the current knowledge of the day.

Key risks to HRT users

HRT has been shown to alter the risk of some cancers and cardiovascular diseases. Depending upon certain risk factors there is an increased risk of developing stroke, venous thromboembolism, breast cancer, ovarian cancer and endometrial cancer.

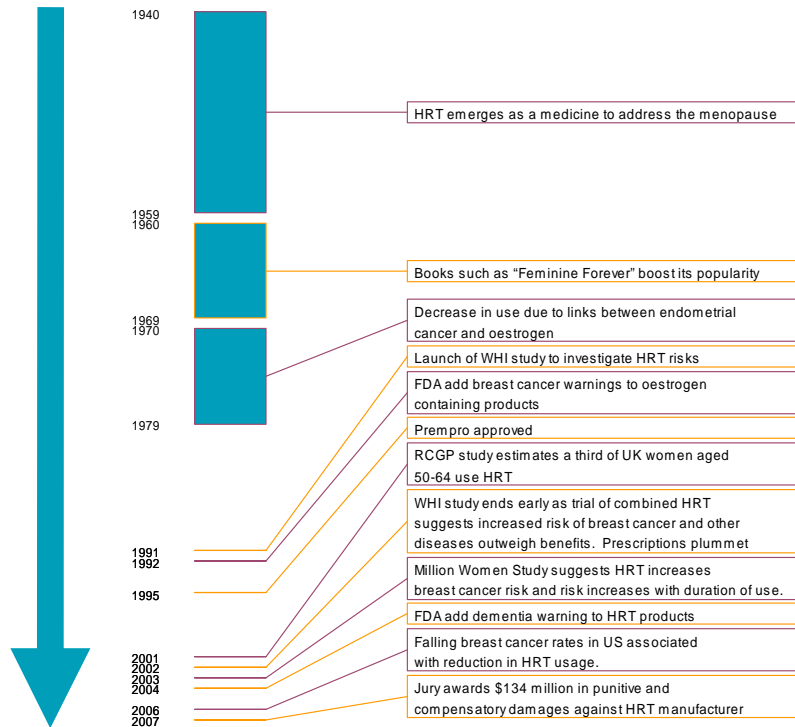
For colorectal cancer there appears to be reduction of the risk, while coronary heart disease risk appears to decrease, stay the same or increase depending upon different risk factors.

It has been shown that HRT can lower the risk of suffering from fractured bones and hence be used to combat osteoporosis. However, given the risks involved in taking HRT, use for treating osteoporosis is typically recommended only if other treatments are not feasible and the benefit in treating the osteoporosis outweighs the risks.

HISTORY – FROM INVENTION TO REGULATION

HRT is an interesting case study for the evolution of an emerging risk and below is a timeline highlighting some key events in the history of HRT.

HRT Timeline



IT IS RECOMMENDED THAT THE SMALLEST REQUIRED DOSE IS GIVEN FOR THE SHORTEST AMOUNT OF TIME

HRT was hailed as a breakthrough treatment for the post-menopausal symptoms and over time its popularity grew as books promoted its symptom relieving and youth giving properties. However, the impartiality of some of the books and media praising HRT was called into question. As time went on scientific research attempted to assess the risks though some results were contradictory and presented a complicated picture.

To resolve the confusion the Women's Health Initiative (WHI) study was commissioned in 1991 to study the risks using a large sample of women. In 2002 it was halted early as a review of the data showed an increase in the risks of breast cancer and cardiovascular diseases. The publication of these results triggered a large reduction in the use of HRT as women were scared off by the increased risk shown by the research. Other studies, including the Million Women Study in UK, corroborated many of the results found by the WHI. While the WHI study has ceased its trials phase, women will continue to be monitored until 2010 and the Million Women Study is also still monitoring its participants. Hence, additional findings on the risks from these large studies may still emerge.

Today, the general consensus is that in most cases the risk/benefit balance for using HRT to combat disease is unfavourable. However, its use to treat post-menopausal symptoms can still be favourable, though it is recommended that the smallest required dose is given for the shortest amount of time.

SUMMARY OF RISK AND DATA

Three key studies have influenced the currently accepted views on the risks of HRT, namely: the Women's Health Initiative (WHI); the Women's Health Initiative Memory Study (WHIMS); and the Million Women Study (MWS). Other important studies also exist, many focusing on a specific area of risk.

There have been concerns that the samples of women used are biased towards certain risk factors, like age or physical health, which can skew the results if not correctly adjusted for. However, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has performed a meta-analysis of international research by statistically combining several studies that tested for the same hypothesis. For each risk the results of key studies are weighted by their importance and averaged to produce a single value for the relative risk. Such a method should help to even out any systematic errors that occur from study to study and reflect a larger sample size (number of women studied). Because of this many of the risk factors quoted in this report refer to the MHRA meta-analysis.

Several diseases have been linked to HRT, where the effect is thought to be positive, negative or debated. To give additional context the table below shows the number of deaths (irrespective as to whether HRT was taken or not) for diseases where HRT is thought to have an impact. Cardiovascular diseases have the biggest associated mortality, though mortality rates from cancer are also high.

Male and female mortality (deaths in 000's in 2002)

Disease	UK	USA	World	UK (%)	USA (%)	World (%)
<i>All causes</i>	599	2,421	57,074	100%	100%	100%
Heart disease	121	514	7,195	20%	21%	13%
Stroke	59	164	5,502	10%	7%	10%
Colon cancer	19	65	621	3%	3%	1%
Breast cancer	15	45	476	3%	2%	1%
Ovarian cancer	4	14	134	1%	1%	0.2%
Endometrial cancer	2	7	71	0.3%	0.3%	0.1%
Venous Thromboembolism	24 ^b	60 ^c	^a	4% ^b	2% ^c	^a

Source: WHO global burden of disease estimates, <http://www.who.int/healthinfo/bodestimates/en/index.html>. a)

No data available, b) House of Commons Health Committee report

<http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/99.pdf>, c) American Heart

Association <http://www.americanheart.org/presenter.jhtml?identifier=4478>

A note on confidence intervals

Scientists often use a concept called “statistical significance”, closely related to “confidence intervals” to decide whether a hypothesis is true or false. As the discussion below will show, the concept of “true or false” is not clear cut and the choice of confidence level can determine the outcome.

An insurer wishing to maintain, and monitor a “radar” of emerging risks may want to keep track of various risks, even if they are considered quite unlikely. For example the current opinion on whether electromagnetic fields cause health issues is highly uncertain. We are not at all confident in the statement “magnetic fields are safe” or in the statement “magnetic fields are dangerous”, but we still wish to monitor the risk. In this example we do not use “high confidence” as the filter; we are more interested in high impact.

The following discussion seeks to illustrate this point taking an example from results published in 2003 by the WHI pertaining to its study on the effect of HRT on breast cancer. They had two groups: those taking combined HRT and those taking a placebo. The number of cases of breast cancer was 245 out of 8,506 women taking the combined pill, and 185 out of 8,102 taking the placebo. The “relative risk” is the ratio of the probabilities of developing breast cancer of the combined group compared to the placebo group. In this example the relative risk is calculated to be 1.26¹. So, based on these raw data, we might conclude that women taking combined HRT had a 26% greater risk of developing cancer over those taking the placebo.

But the estimated probabilities are based on sample data and are subject to random fluctuation. The smaller the group being tested, the more likely randomness will distort the results. The true underlying probabilities might not be different at all but may appear so due to random results. We might conclude the risk has increased when it has not.

The confidence interval can be estimated by making assumptions about the distribution of results from a random sample. In this example a 99% confidence interval for the relative risk is 0.98 to 1.62, which we can write as (99% CI, 0.98-1.62). In other words we can be 99% confident that the true value of the relative risk lies between these two values.

To conclude, with 99% confidence, that the relative risk of developing breast cancer in this case is above “normal levels” the entire confidence interval must be above 1.0. In this case it is not (0.98<1.0). So we are *not* 99% confident that the risk of breast cancer is increased. However, with 95% confidence the confidence interval shrinks to (1.04-1.52) and this would be considered statistically significant. We are 95% confident the risk has increased. Many scientists like to be at least 95% certain before drawing a conclusion; but insurers might wish to monitor risks that are less certain, in case more information comes to light later.

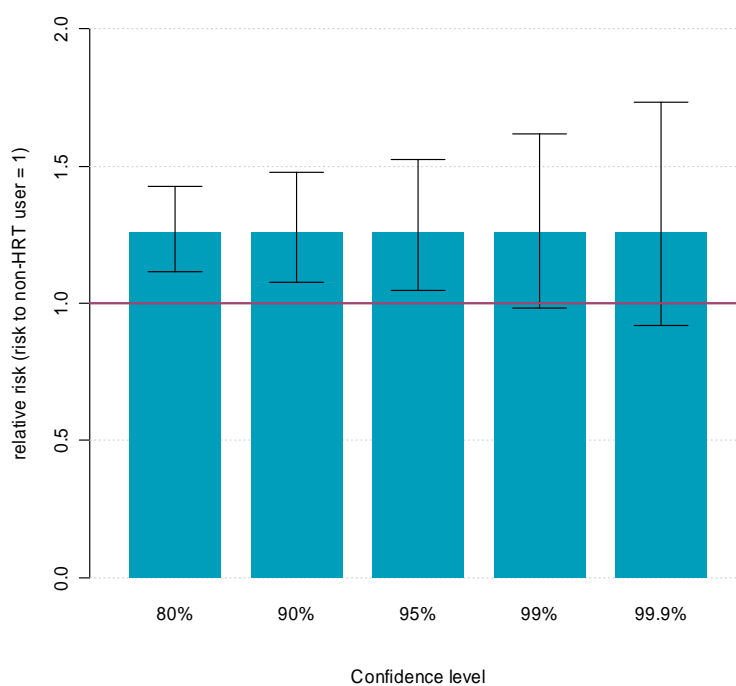
The key message is that we may wish to include risks for monitoring purposes that other groups have concluded are not significant.

WE MAY WISH TO INCLUDE RISKS FOR MONITORING PURPOSES THAT OTHER GROUPS HAVE CONCLUDED ARE NOT SIGNIFICANT

¹ Relative risk formula; $\frac{245/8506}{185/8102} = 1.26$

The diagram below shows the effect of changing the confidence level from 80% to 99.9% for the breast cancer example. The confidence interval is indicated by the vertical bars. When the required level of confidence is increased the width of the confidence interval also increases. In other words to be more confident we must admit a wider range of possibilities. The underlying data behind these numbers remains unchanged; it is only the level of confidence that is altered.

Effect of confidence level on confidence interval

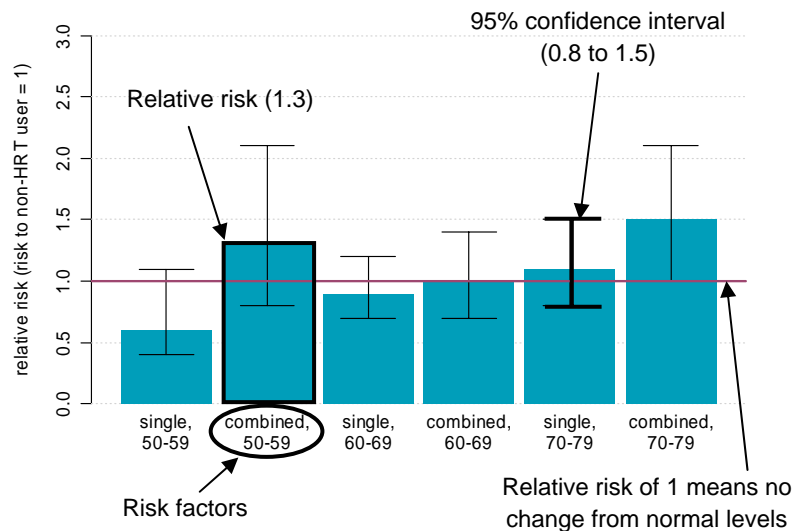


A common confidence level used by papers discussing HRT is 95%. Therefore, the following sections will present the data with their 95% confidence intervals. However, one section will consider other confidence levels to illustrate that some risks, whilst they may not be considered significant by health professionals, are still of relevance to insurers.

Diseases

The following sections group “disease” into: cardiovascular; cancer; and other, and will provide a brief introduction to each. If applicable, a chart will show the relative risk to an HRT user, an example of which is shown below and annotated to show how the various components of the chart should be read.

Example of relative risk diagram



The chart indicates the 95% confidence intervals, relative risk values and risk factors. Risk factors considered are:

- age of patient;
- duration of HRT use; and
- type of HRT used.

A risk is not affected by a risk factor if it is not shown. The type of HRT used is abbreviated to either “single” (oestrogen only) or “combined” (oestrogen and progesterone). If a relative risk is below 1.0 this indicates a reduced risk, while a risk factor above 1.0 indicated an increased risk

Relative risk in context

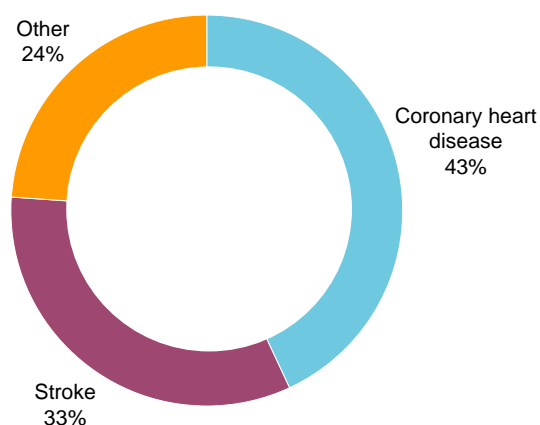
For context, according to the Centers for Disease Control and Prevention (CDC), the relative risk factor of developing lung cancer for someone smoking cigarettes is about 10 to 20. The highest relative risk according to the MHRA meta-analysis is for women who have not had a hysterectomy taking oestrogen, ranges from 3 to 9. Breast cancer risk ranges from 1.2 to 2.2. So the relative risk of developing a single disease from using HRT is currently estimated to be lower than the relative risk of developing lung cancer from smoking.

Cardiovascular diseases – an overview

Cardiovascular diseases (CVDs) are diseases associated with the heart and blood vessels, including:

- Coronary heart disease (CHD)
- Cerebrovascular disease (stroke)
- Raised blood pressure (hypertension)
- Peripheral artery disease
- Rheumatic and congenital heart disease
- Heart failure
- Venous Thromboembolism (VTE)

Global cardiovascular mortality (17.5m deaths)



Source: World Health Organisation, Fact sheet No. 317, February 2007

**WITHIN AROUND 3 YEARS
OF CEASING TREATMENT
CARDIOVASCULAR RISKS
APPEAR TO RETURN TO
NORMAL LEVELS**

The major risk factors for CVDs are tobacco use, physical inactivity and an unhealthy diet. These factors contribute to fatty build-ups in blood vessels, which cause restriction of blood flow. The World Health Organisation (WHO) states that CVDs are the number one cause of death globally, killing 17.5 million people in 2005 worldwide. In both Europe and the USA cardiovascular diseases (CVDs) cause between 35% to 40% of all deaths in both men and women, a break of the contribution of the different diseases by mortality is shown below.

HRT has been identified as a potential risk factor of coronary heart disease, stroke and venous thromboembolism. The decision by academic studies to investigate these diseases, and indeed the other diseases associated with HRT, appears to be to:

- validate the beneficial health claims made of HRT over the years;
- clarify the sometimes contradictory research findings; and
- launch a general investigation into women's health.

However, as only a specific set of diseases were investigated there could be other diseases where HRT is a risk/benefit factor. The risks associated with cardiovascular diseases have been observed to change due to taking HRT. However, within around 3 years of ceasing treatment the risks appear to return to normal levels according to the main studies.

Coronary Heart Disease

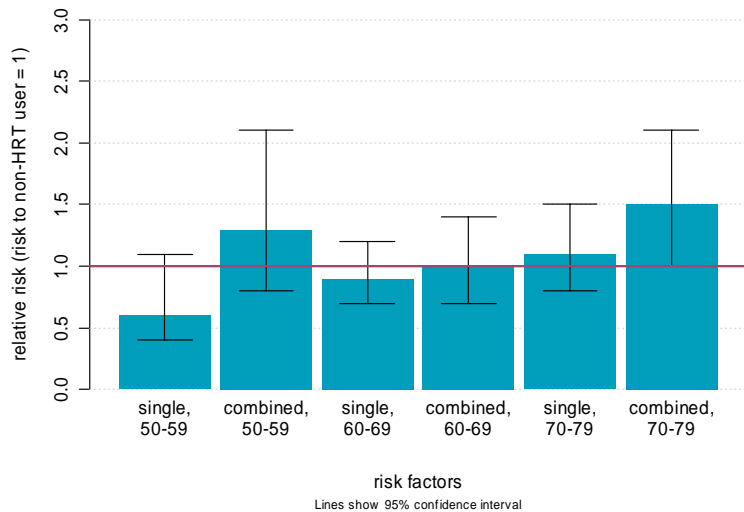
Globally, of the 17.5 million people who died from cardiovascular diseases in 2005, approximately 7.6 million (43%), were due to coronary heart disease (CHD). This makes CHD the most common form of cardiovascular disease, and in the EU and USA it accounts for approximately one in six of all deaths.

CHD is where the blood vessels that supply the heart become damaged, weakened or contain a build up of fatty deposits. This can lead to a restriction of blood supply causing damage to the heart or a heart attack.

The MHRA meta-analysis shows that the effect on CHD varies depending upon age and type of HRT, though none demonstrate significance beyond a 95% confidence interval. However, if considering a lower confidence interval there are 3 groups of factors that indicate a changed level of risk: Women aged 50-59 taking oestrogen (single) HRT appear to have a lower risk; women taking combined HRT aged 50-59 or 70-79 appear to have an increased risk; while for the remaining groups the risk appears relatively unchanged.

However, as the risk of developing CHD is already high, any small changes in the relative risk can lead to a large change in the absolute risk and hence the number people affected.

Effect of HRT on coronary heart disease



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

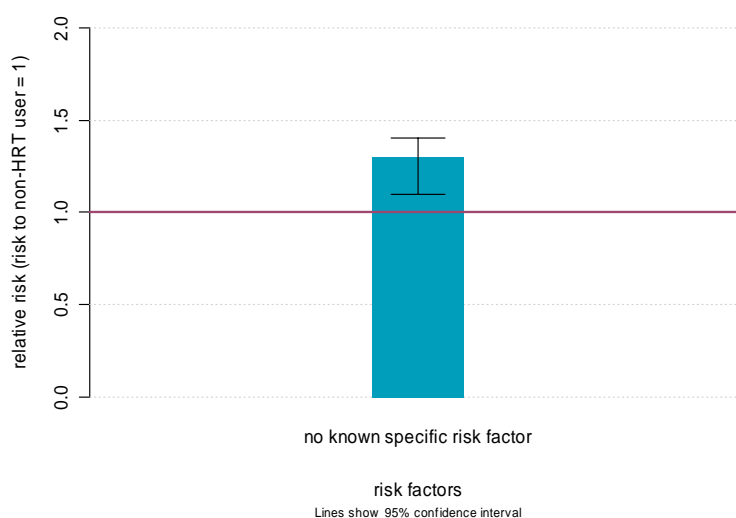
It has been suggested that the effect of HRT on CHD may depend upon the vasculature (blood vessel system) health of the patient. HRT could have a protective effect for a healthy vasculature, no effect for those with a mild to moderately unhealthy vasculature and a damaging effect for those with an unhealthy one. Most studies, however, focus on older women so there is little evidence to support a cardio-protective effect in younger women. This demonstrates why it's important for doctors to consider a prospective HRT user's needs on a case by case basis.

Strokes (Cerebrovascular Disease)

Like CHD, strokes are typically triggered by blood clots obstructing vessels, but in this case the organ affected is the brain. Major risk factors include tobacco use, physical inactivity and an unhealthy diet. Survivors of strokes can exhibit several symptoms including weakness or numbness of the face or limbs, difficulty speaking or understanding speech, confusion and sight impairment.

Strokes account for 5.7 million of the 17.5 million (33%) annual CVD deaths, or approximately 10% of all deaths globally. This makes strokes the second most common form of CVD.

Effect of HRT on stroke risk



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

The MHRA meta-analysis shows that HRT raises the risk of stroke by about 30% (relative risk factor of 1.3). The confidence interval shows that the increased risk has well over a 95% of not being due to chance. The risks appear to be independent of age (50+), duration (5+ years) and whether the prescription is single or combined.

Venous thromboembolism

Venous thromboembolism (VTE) is when a blood clot forms within a vein (Venous thrombosis), becomes dislodged and causes a blockage in a vein elsewhere within the body. If the blood clot forms in the deep veins within the legs, thighs or pelvis it is known as deep vein thrombosis (DVT). A blockage can cause a pulmonary embolism (PE) where the arteries to the lung are blocked and hence the body is starved of oxygen.

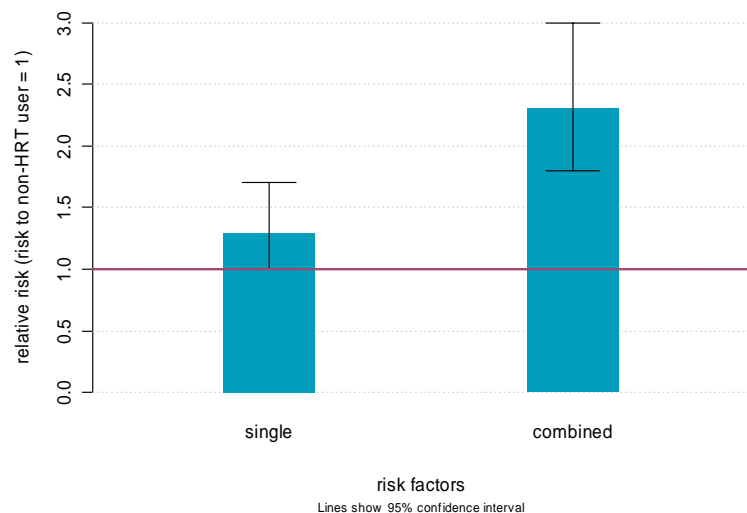
Risk factors for VTE include:

- increasing age;
- prolonged immobility, stroke or paralysis;
- previous VTE;
- cancer and therapeutic interventions;
- major surgery;
- trauma;
- obesity;
- varicose veins;
- cardiac dysfunction;
- central venous catheters;
- inflammatory bowel disease;
- nephrotic syndrome; and
- pregnancy or hormonal therapy use.

The MHRA meta-analysis shows that HRT introduces an increased risk, with 95% confidence, regardless of age or duration of use, and that combined HRT more than doubles the risk of VTE.

Effect of HRT on venous thromboembolism

COMBINED HRT MORE THAN DOUBLES THE RISK OF VTE



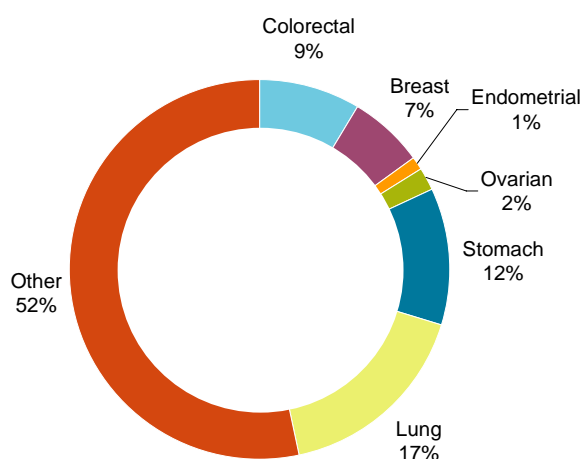
Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

Figures on global deaths due to VTE are difficult to quantify, but approximately 24,000 people a year die as a result of a VTE in the UK, and 60,000 in the USA. According to a UK House of Commons report the precise numbers of deaths are difficult to gauge as many deaths are not followed up by a post mortem and, hence, the number of deaths attributed to VTE is probably an underestimate.

Cancer – an overview

According to the WHO cancer is a leading cause of death globally. It estimates that 7.9 million people died as a result of cancer in 2007, or approximately 13% of all deaths. Cancer is triggered by a single cell malfunctioning leading it to multiply and grow uncontrollably. It can affect any part of the body, though among women the most commonly affected areas are the breasts, lungs, stomach, colon and cervix. Below is a chart indicating the proportion of global deaths due to differing types of cancer.

Global cancer mortality (7.3m deaths)



Source: World Health Organisation, Fact sheet No. 297, July 2008

There are many risk factors linked to developing cancer, though the WHO estimates that 30% of cancers can be prevented. The key preventable risk factors are:

- tobacco and alcohol use;
- obesity, poor diet and physical inactivity;
- sexually transmitted diseases; and
- urban air pollution and smoke from burning solid household fuels.

Other risk factors include an individual's genetic susceptibility and age, being exposed to UV and ionising radiation, certain chemicals, such as asbestos or arsenic, viruses, bacteria and parasites.

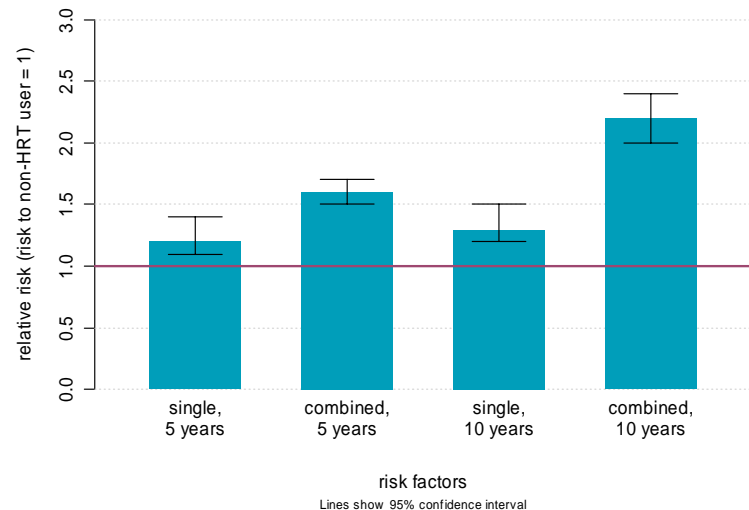
WITHIN 5 YEARS OF STOPPING THE TREATMENT THE RISK FALLS BACK TO NORMAL

Breast Cancer

Breast cancer killed 548,000 people worldwide in 2007 and is the most common form of cancer in women. According to Cancer Research UK approximately 44,500 people are diagnosed in the UK annually with breast cancer with the vast majority being women - only about 300 are men. In 2004 in the UK there were 121 cases per 100,000 women, and of the new cases 4 out of 5 were aged 50 and over. When broken down by age the incidence rate was 303.7 per 100,000 for women aged 50-64 (0.30% per annum) increasing to 356.7 per 100,000 for women aged 70+ (0.35% per annum).

In the US it is estimated by the American Cancer Society that the number of new cases in women will be 182,460 in 2008. The incidence rate in 2004 for women aged 50+ was 340 per 100,000 women (0.34% per annum). The MHRA meta-analysis shows that the risk increases with how long a woman takes HRT and whether the prescription is single or combined, though not with age. However, within 5 years of stopping the treatment the risk falls back to normal.

Effect of HRT on breast cancer



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

The clear increase in relative risk combined with the already high incidence rate among women results in a higher absolute risk, and the physiological impact of developing breast cancer makes this risk even more significant than others. This most likely explains why the majority of legal claims to date have involved breast cancer. According to the Million Women study:

“Use of HRT by women aged 50-64 years in the UK over the past decade has resulted in an estimated 20,000 extra breast cancers, 15,000 associated with oestrogen-progestagen; the extra deaths cannot yet be reliably estimated”

At around 2,000 additional cases per year, this equates to approximately 4.5% of all breast cancers in the UK being caused by women taking HRT. However, identifying HRT as the direct cause can be problematic as breast cancer can be caused by a number of other factors. Evidence also indicates that taking HRT, particularly combined HRT, can interfere with breast cancer screenings leading to an increased rate of misdiagnosis. This could have a compounding effect where both the risk of breast cancer and the chance of it not being caught, and therefore treated, increases.

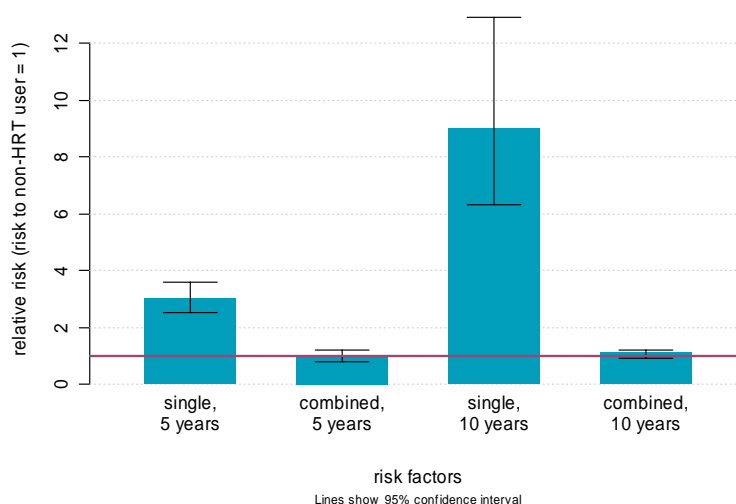
“USE OF HRT BY WOMEN AGED 50-64 YEARS IN THE UK OVER THE PAST DECADE HAS RESULTED IN AN ESTIMATED 20000 EXTRA BREAST CANCERS”

THE HORMONE PROGESTERONE COUNTERS THE RISK TO ENDOMETRIAL CANCER CAUSED BY TAKING OESTROGEN

Endometrial Cancer

In the UK during 2005 there were 6,430 women diagnosed with endometrial cancer, or cancer of the womb, while in the USA there are expected to be an estimated 40,100 new cases in 2008. There has long been broad consensus that patients who take oestrogen alone have an increased risk of developing endometrial cancer. It is also known that the hormone progesterone reduces this risk. This is the reason why HRT is typically prescribed as a combination of these hormones. The main exception to this is when a woman has had her womb removed through a hysterectomy. In this case the cancer cannot occur and oestrogen is prescribed on its own to remove any risks that progesterone may introduce.

Effect of HRT on endometrial cancer



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

The MHRA meta-analysis clearly shows the increased risk of developing endometrial cancer when taking oestrogen-only HRT. The data also shows the risk reduction effect of adding progesterone to oestrogen as the relative risk of the combined therapy is brought back down to normal levels.

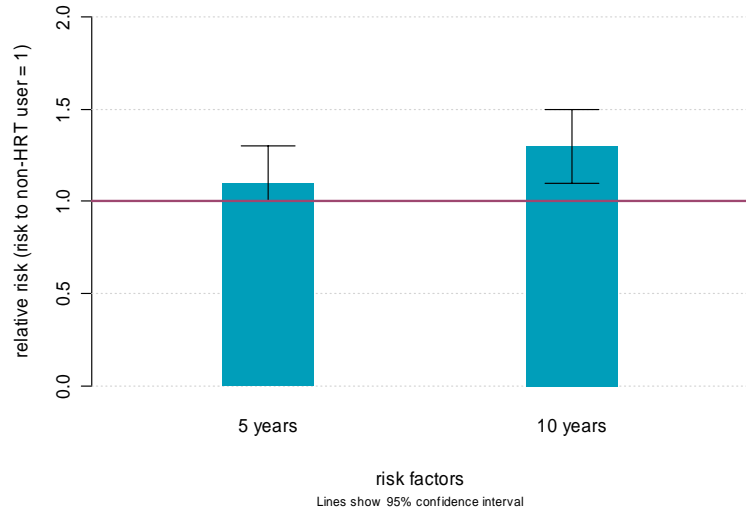
Ovarian Cancer

In the USA, cancer of the ovaries is estimated to affect an additional 21,650 women in 2008, while in the UK about 6,600 women are diagnosed each year.

The MHRA meta-analysis shows that taking HRT, single or combined, leads to an increased risk of ovarian cancer with at least 95% confidence. It also indicates that the longer HRT is taken, the higher the risk.

Effect of HRT on Ovarian cancer

“SINCE 1991, USE OF HRT HAS RESULTED IN SOME 1,300 ADDITIONAL OVARIAN CANCERS AND 1000 ADDITIONAL DEATHS”



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

In 2006 a paper published by The Million Women Study stated that “Women who use HRT are at an increased risk of both incident and fatal ovarian cancer. Since 1991, use of HRT has resulted in some 1,300 additional ovarian cancers and 1,000 additional deaths from the malignancy in the UK.”

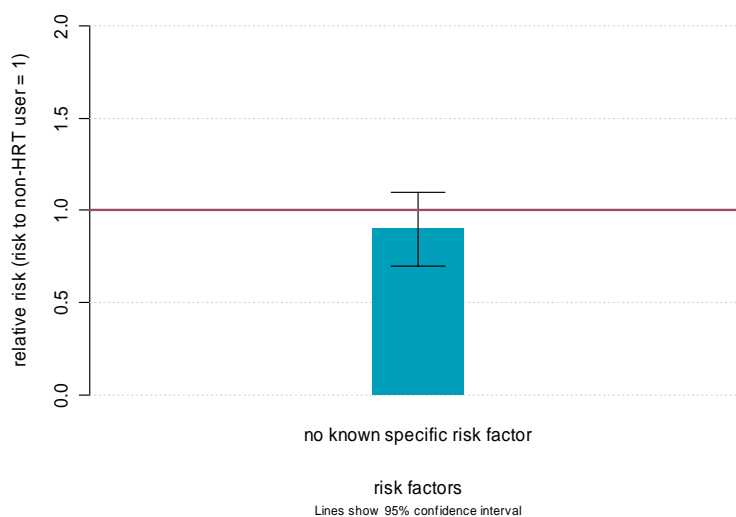
This approximates to 1.3% of all new cases of ovarian cancer in the UK are being due to HRT since 1991.

Colorectal cancer

Colorectal cancer, also known as bowel cancer, is estimated to affect 108,070 additional people in the USA in 2008. In the UK, women account for 13,389 new cases each year, men for 21,617.

The MHRA meta-analysis indicates that the risk is reduced, though with a confidence of less than 95%. The risk also seems to be independent of risk factors such as type of HRT, length of usage and age.

Effect of HRT on colorectal cancer



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

Cancer Summary

While the risk of colorectal cancer appears to reduce, the overall effect of HRT is to increase the risk of developing many types of cancer. In addition, according to the National Institute of Health (NIH), once HRT treatment ceases the risk of developing colorectal cancer returns to normal. However, the combined risk of developing all cancers remains elevated compared to those who never took HRT.

TAKING HRT CAN REDUCE THE CHANCE OF SUFFERING A BONE FRACTURE BUT IS ONLY RECOMMENDED AS A TREATMENT OF LAST RESORT

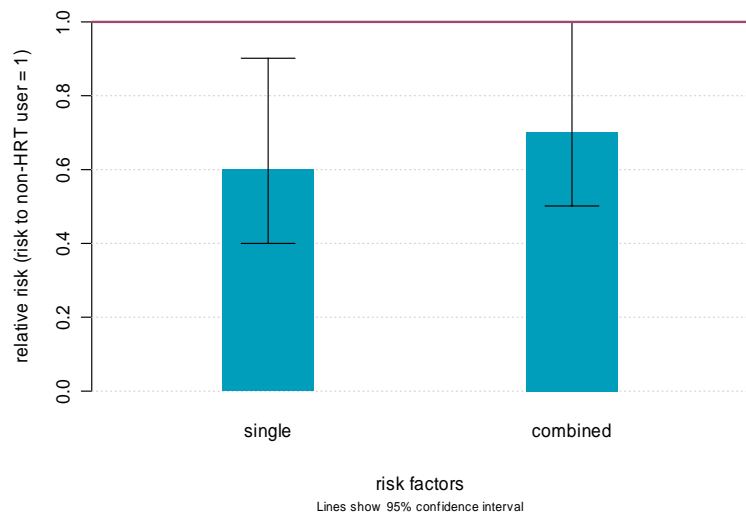
Other diseases and concerns

There are some other concerns and perceived benefits to HRT, which include dementia, arthritis and prevention of osteoporosis.

Prevention of Osteoporosis

Osteoporosis is the deterioration of bone mass and is typically associated with aging. The MHRA meta-analysis indicates that taking HRT can reduce the chance of suffering a bone fracture and hence combat osteoporosis. Regulators and health professionals have recognised this reduction, though it is only recommended as a treatment of last resort due to the other risks associated with HRT.

Effect of HRT on fracture of femur



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

Dementia and Alzheimer's Disease

According to the Alzheimer's Society, Alzheimer's disease is the most common cause of dementia, affecting around 417,000 people in the UK. Symptoms include confusion, memory loss and mood swings.

Because some animal studies involving hormones were observed to maintain and protect the brain it was thought that HRT could offer a similar benefit to humans. However, following the initial results of the Women's Health Initiative Memory Study (WHIMS), a sub-study of the WHI, there were concerns that HRT could increase the risk of dementia and Alzheimer's disease. The reported relative risk of probable dementia was 2.05 with a 95% confidence interval of 1.21 to 3.48. This resulted in the FDA recommending that manufacturers include warnings on their products. However, recent repeated studies indicate that there is no link, and a recent paper entitled "Hormone replacement therapy for cognitive function in postmenopausal women" concluded that:

"There is good evidence that oestrogen or combined oestrogen and progesterone therapy does not protect against a decline in overall cognitive functioning of older postmenopausal women with normal intellectual ability."

Arthritis

Rheumatoid arthritis is caused when the immune system attacks the lining of joints. This results in swelling, inflammation and pain, which can lead to permanent damage and disability. It affects around 350,000 people in the UK and 1.3 million in the US, and is more commonly found in women than men.

Along with osteoporosis, development of arthritis is associated with the menopause, hence, investigations have been undertaken to examine the effect of HRT on arthritis.

A recent study using data from the WHI study has concluded - with 95% confidence - that there is no increased risk of developing rheumatoid arthritis or an increase in its severity for users of HRT. The relative risk of developing rheumatoid arthritis was 0.74 with a 95% confidence interval between 0.51 and 1.10. With a lower confidence level the risk may be interpreted as reduced. This study did not break down this number by risk factors such as age, period of use or type of HRT, and therefore it cannot be compared directly to the MHRA meta-analysis.

Bio-identical hormone replacement therapy

Marketers of compounded bio-identical hormone replacement therapy (BHRT) have come under fire from the US regulator the Food and Drug Administration (FDA). BHRT uses hormones that are alleged to be identical to those within the human body, while compounding is the practice of mixing several drugs together to produce a tailor made drug specifically for an individual patient. The FDA released a statement in early 2008 declaring that claims such as "A natural, safer alternative to dangerous prescription drugs", "Can slim you down by reducing hormonal imbalances"; "Prevents Alzheimer's disease and senility" are unproven. They are concerned that these will "mislead women and health care professionals, giving them a false sense of assurance about using potentially dangerous hormone products." They specifically highlight pharmacies that offer their own compounded BHRT with unsupported claims.

As far as the FDA is concerned they do not recognise BHRT as a marketing term and have not approved any compounded BHRT drugs saying that "one of the big problems is that we just don't know what risks are associated with these so-called 'bio-identicals'."

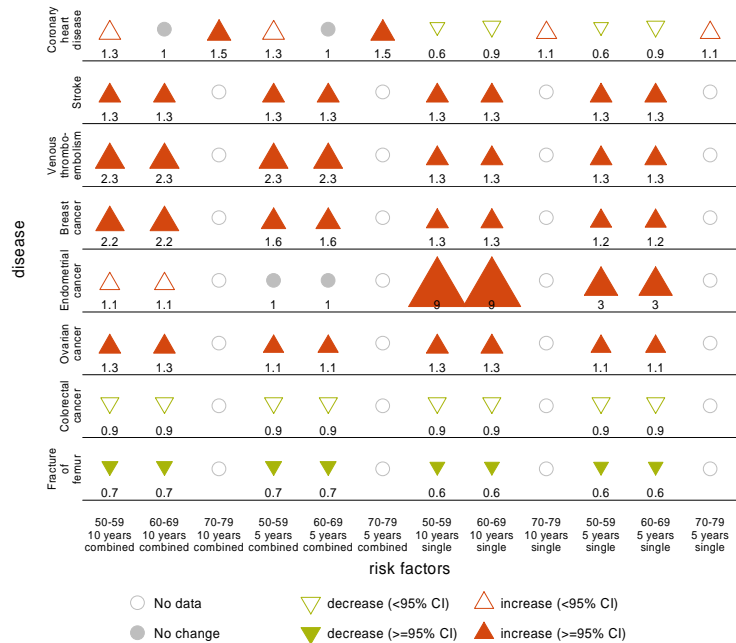
"WE JUST DON'T KNOW WHAT RISKS ARE ASSOCIATED WITH THESE SO-CALLED 'BIO-IDENTICALS'"

Risk/Benefit Balance

In terms of disease prevention the general consensus is that on the whole the adverse consequences of taking HRT outweigh the benefits. This is a generalisation as the risk will depend on an individuals own risk factors such as susceptibility to certain diseases, age and weight.

Relative risk for diseases and risk factors

THE GENERAL CONSENSUS IS THAT THE ADVERSE CONSEQUENCES OF TAKING HRT FOR DISEASE PREVENTION OUTWEIGH THE BENEFITS



Source: MHRA, HRT: safety update – UK Public Assessment Report, September 2007

The chart above summarises the MHRA meta-analysis. The biggest effect of oestrogen only (single) therapy is the increased risk of developing endometrial cancer. This risk is controlled through the use of combined therapy, though several risks such breast cancer, VTE and CHD have increased.

In a letter to doctors the MHRA summarised their view on risk/benefit balance as:

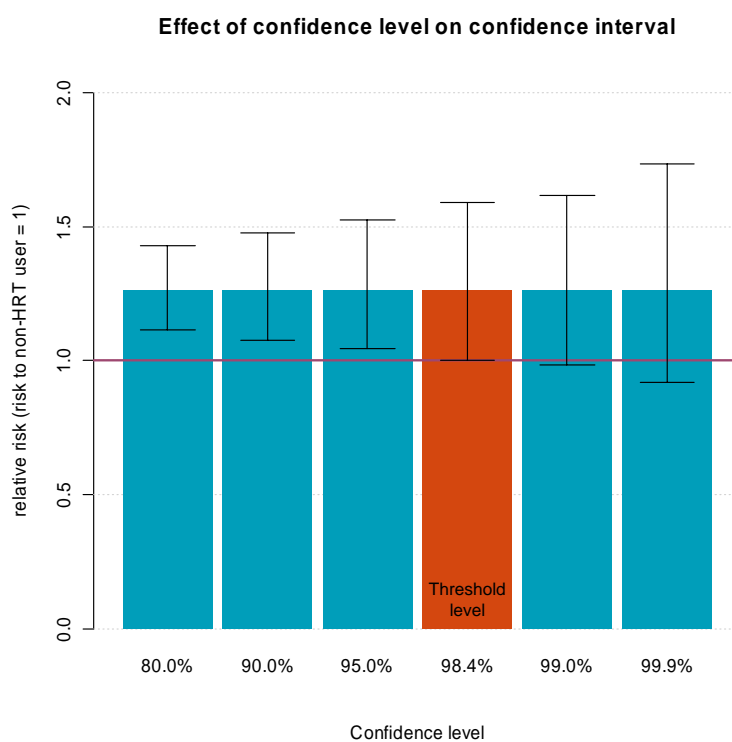
- The risk/benefit of HRT is favourable for treatment of menopausal symptoms. The minimum effective dose should be used for the shortest duration.
- The risk/benefit of HRT is unfavourable for the prevention of osteoporosis as first-line use.
- In healthy women without symptoms, the risk/benefit of HRT is generally unfavourable.

Confidence summary

As an aside it is interesting to examine the effect of confidence level chosen in the charts presented in the previous sections. They were all presented with a 95% confidence level, in line with common practice. However, an estimate¹ can be found for the confidence level at which the bounds of the confidence interval crosses the “normal” risk threshold, which has a value of one.

The following chart is identical to that shown on page 11, except that it also includes an extra confidence level, labelled the “Threshold level”. In the example chart below the risk can be said to be increased from normal levels with 80, 90 and 95 percent confidence, but not with 99 or 99.9 percent confidence. Therefore there is a threshold level between 95 and 99 percent where confidence in the risk increase begins, which in this case it is 98.4 percent.

Effect of confidence level on confidence interval, including the threshold confidence level



The chart on the next page shows the threshold confidence level for each disease and risk factor combination.

REGULATION

Advice for the prescription of HRT to women in the USA and EU is similar and follows these general themes:

- To be used primarily for relieving the symptoms of the menopause and not for the prevention of diseases.
- Risk of developing a number of diseases are elevated and therefore it should be administered for the shortest possible time using the smallest possible dose.
- HRT is typically only suitable for treating osteoporosis when other options have been exhausted.
- Ultimately the risks and benefits will be unique to each patient and the best course of treatment should always be discussed with a doctor.

This advice allows HRT to continue to be used. However, by taking an individual's unique situation into account doctors and patients can now make more informed decisions compared to 10 or 20 years ago thanks to the major studies published since 2002.

Looking at the MHRA meta-analysis there still appears to be areas in which additional research could reduce the uncertainty regarding the relative risk factors. Indeed the Royal College of Obstetricians and Gynaecologists (RCOG) recommend 24 areas of research to be investigated, including:

- To identify dosages and routes of administration of oestrogen alone or combined oestrogen plus progesterone preparations that do not increase breast cancer risk, while still retaining fracture benefit.
- To identify further areas where HRT may have an impact on quality of life, e.g. urogenital prolapse, urinary incontinence and sexual dysfunction.
- To examine whether women shown to have increased mammographic density as a result of HRT should consider temporarily stopping treatment for a period of time before attending for mammographic screening.

The first recommendation indicates that advancements in HRT delivery could lead to an improved risk/benefit balance; the second highlights that there could be further impacts beyond those already researched; while the third shows concern that HRT could affect screening results.

INSURANCE IMPACTS

The main issue lies in the concern of patients that they were misled by manufacturers advertising of HRT, the use of which they believe has caused them harm, typically in contracting breast cancer. Compensation is typically sought from the manufacturers arguing that if they had the full risk/benefit analysis available to them they would not have taken HRT and hence would not have developed any ill effects.

The following scenarios are either currently occurring or are a possibility:

- **Product liability.** Manufacturers are a target for litigation by users of HRT for providing misleading information regarding their products leading to the patient being unaware of the full set of risks and benefits known at the time. Manufacturers could become a target for lawsuits for not testing their product thoroughly enough, or for intentionally misleading patients. This could affect **general and product liability** policies.
- **General liability.** Patients may make Medical Monitoring claims, whereby patients who are put at increased risk of diseases due to a drug sue manufacturers for the costs of monitoring for the development of those diseases. The additional monitoring would aim to increase the chances of early disease detection and hence mitigate the potential negative consequences of taking the drug. This could trigger **general liability** policies for the manufacturers, though this type of claim is largely untested against pharmaceutical products.
- **Medical Malpractice.** Medical professionals could be a target for litigation, affecting **Medical Malpractice** policies. Hospitals too could be a target if they have general policies advising their employed practitioners on how to prescribe HRT. However, if manufacturers were found to be the source of misleading advice they may become liable through subrogation. To date there appears to be very little legal activity in this area. This is most likely due to the expected claims being lower in value compared to claims against manufacturers, where large classes can be brought and the limits on the insurance policies can be higher.

Within the US a lawsuit must be filed within 1 to 6 years, depending upon the state. Hence, the date at which the disease manifested itself and the date at which a patient could have been reasonably expected to know of the link with HRT are important. In the case of *Simon v. Wyeth* and *Coleman v. Wyeth* this issue was raised. In the *Coleman v. Wyeth* case the judge ruled that the 2002 WHI study could not be used as the discovery date and cited several media reports going back to 1997 as examples of evidence preceding it. The way in which insurance policies will respond to these issues will be determined by whether it is a “*losses occurring*” or “*claims made*” form.

What follows is a brief outline of some of the more recent legal cases involving HRT since 2006.

LEGAL CASES TO DATE

The majority of lawsuits are US based and involve women suing the pharmaceutical company Wyeth for personal injury. Wyeth is a large manufacturer of several HRT products including Prempro and Premarin, and the women claim that these products caused their development of breast cancer. Wyeth is not the sole manufacturer of HRT, though according to a review article in the British Medical Journal, in 2003 Wyeth had more than a 70% share of the global market.

As of December 2007 Wyeth faces 5,400 actions brought on behalf of 7,900 women and several presented here are acting as test cases. The following cases have been brought in Pennsylvania, New Jersey, Arkansas, Florida and Nevada. The American Tort Reform Association place South Florida, New Jersey and Nevada in their top 6 places in the US that are considered to be aggressive against defendants in civil lawsuits such as those against HRT manufacturers.

Cases currently in favour of the manufacturers (defendants)

- Considering the cases of Coleman v. Wyeth, Bailey v. Wyeth, DeBoard v. Wyeth and Reeves v. Wyeth et. al., brought in Pennsylvania, New Jersey and Arkansas. The evidence provided by the plaintiff, those seeking compensation, was not enough to show that the defendant did not comply with all of its regulators requirements when labelling their products, or that they manipulated the post-market regulatory process.
- In order to prove proximate causation some plaintiffs have been asked to prove that if labelling were improved a plaintiff's doctor would not have prescribed HRT. This test has failed in several cases in Pennsylvania such Nelson v. Wyeth and Simon v. Wyeth, though these are on appeal to the Superior Court. One judge said the manufacturer only has a duty to inform the doctor, and not the patient, of potential risks as it is the doctor's role to apply these to their patient's individual risk factors.
- Several cases have been dismissed as the plaintiff did not file a lawsuit within the legally required time period. A time limitation rule is common in personal injury cases and in Coleman v. Wyeth and Simon v. Wyeth the limit was two years. The plaintiffs argue that the publication of the WHI study in 2002 should have been the trigger for the two year countdown. However, the judge ruled that the plaintiff was informed by labelling, information given by her doctor and media publications at the time of diagnosis in 2000. In addition, several media reports published from 1997 onwards were presented showing the link between breast cancer and HRT. Hence, they could not use the discovery rule to "reset the clock" as the plaintiff's was believed to have enough information to make the link between HRT and their breast cancer at the time of diagnosis, and not in 2004 when the case was filed. It is possible that similar cases will not be able to use the WHI study as the event of discovery as a result of this ruling.

- In *Wyeth v. Gottlieb*, a Florida appeal court prevented a state-wide Medical Monitoring class action from being certified. A Medical Monitoring claim seeks payment for the costs of tests to diagnose for specific diseases. This type of claim was conceived to help those who were exposed to harmful substances, through employment or pollution, which elevated the risk of developing specific diseases. This type of claim was designed for people exposed to toxic chemicals but is now being tried against prescription drugs. There are several hurdles to overcome if this to become common practice, but the uncertainty as to whether this type of claim is valid appears to be fuelling the filing of lawsuits.

Cases currently in favour of patients (plaintiffs)

- *Wyeth* lost its bid to block a Canadian lawyer's request to file a lawsuit against it. *Wyeth* had argued the US based company was beyond the jurisdiction of the Canadian women. The lawsuit can now apply to become a class-action allowing other women from Canada to join its representative plaintiff, Dianna Stanway, who alleges she contracted breast cancer after taking Premarin.
- In *Scroggin v. Wyeth* the plaintiff was awarded \$2.75 million compensation by an Arkansas jury, after accusing the defendant of negligence in providing her with appropriate warning of the increased risk of breast cancer. A punitive award of \$27 million was initially given; however, this was later thrown out by a federal judge, rejecting the evidence given by the plaintiff's expert witness. *Wyeth* is now also appealing against the compensation award.
- A trial in Reno, Nevada awarded three women a total of \$99 million dollars in punitive damages and \$35 million in compensation against *Wyeth*. The women claimed that taking HRT caused their breast cancer and that *Wyeth* did not fully investigate the effects of their drugs even after several "red flags" were raised since the 1970's. The manufacturer felt the award was excessive and, after appeal, this was reduced to \$35 million in punitive damages and \$23 million in compensation. This was the largest against *Wyeth* at the time of trial, and *Wyeth* is still appealing to overturn the judgement entirely, arguing that their drugs were FDA approved and that information on the risks was provided to doctors and with the drug.

Summary

Several of the cases highlighted above are on appeal and hence awards may be subject to change. There are some cases where the manufacturers initially lost but the appeal courts later reduced the payout or reversed the decision, such as *Scroggin v. Wyeth* and *Coleman v. Wyeth*.

The Reno case highlights that large awards are possible. However, there is a pattern of high punitive damages being awarded against defendants that later get overturned or reduced on appeal.

There is still no definitive answer to whether HRT manufacturers will be found ultimately liable for the risks of HRT and given the number of cases pending it is important for all concerned to watch any developments closely.

CONCLUSIONS

Research carried out over the last decade has identified and evaluated the risks associated with HRT. It has been shown to increase the risk of several diseases. Nevertheless, it is still deemed suitable for treating women with severe symptoms of the menopause with the advice of their doctor.

The biggest concern lies in the effect of HRT on the development of breast cancer due to the combination of several factors including:

- high normal breast cancer incidence rate, so the number of people affected by this disease is high to start with;
- the additional risk caused by HRT is significant, in other words there is a higher relative risk; and
- unlike some diseases where the increased risk only affects certain groups, the risk of developing breast cancer is increased regardless of age, duration of use and HRT type.

The result is an increased absolute number of HRT users developing breast cancer. Stroke also has these factors in common, although the relative risk factor is not so high and to date there seems to be little legal activity in this area.

As far as we are aware there is no definitive method to prove that taking HRT caused an individual person to develop a disease. However this has not stopped damages being awarded to women seeking to sue manufacturers for compensation due to the increased susceptibility caused by using HRT.

The majority of legal cases are waiting for the outcome of the current test cases, and several routes are being tried that include legal action based on:

- insufficient or misleading labelling or advertising;
- attempting to claim for medical monitoring costs; and
- neglect in duty of care to fully investigate risks of the drug before sending to market.

Some cases have been successful, resulting in high punitive damages; however, many had awards reduced or overturned on appeal. For the purposes of risk tracking, the results of current and future legal cases should be watched closely for major developments.

GLOSSARY

Below are a list of terms and abbreviations used in this report. Many definitions and descriptions are taken from learned and respected organisations working in health, statistics or insurance. The legal terms in this glossary are based on American definitions as the majority of legal cases quoted in this report are based in the USA.

Arthritis

Arthritis is a term used to describe a number of painful conditions of the joints and bones. Two of the main types of arthritis are osteoarthritis and rheumatoid arthritis. Rheumatoid arthritis results in the body's immune system attacking and destroying the joint, causing pain and swelling. It can lead to reduction of movement, and the breakdown of bone and cartilage.

Bio-identical hormone replacement therapy (BHRT)

According to the FDA, BHRT purports to be a type of HRT that uses hormones that are identical in chemical form to those used by the human body. The term has come under fire from the FDA as the term "bio-identical" implies a lower risk than other HRT, though no evidence exists to support this claim.

Cardiovascular diseases (CVD)

Cardiovascular diseases include coronary heart disease (heart attacks), cerebrovascular disease (stroke), raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease, heart failure and venous thromboembolism. The major causes of cardiovascular disease are tobacco use, physical inactivity, and an unhealthy diet.

Centers for Disease Control and Prevention (CDC)

Part of the U.S. Department of Health and Human Services, it is the primary Federal agency for conducting and supporting public health activities in the United States.

Clinical trials

According to the US Department of Health and Human Services clinical trials control and compare specific medical interventions, such as the use of HRT. Women on an intervention are compared with those who do not receive the treatment. Researchers try to control all of the experimental conditions so that any difference between the two groups can be tied to the intervention.

The most rigorous of these investigations is the randomized, controlled, double-blind clinical trial. Women are randomly assigned to the study groups and, in a drug trial for instance, neither the women nor the researchers typically know who is receiving an active drug or a placebo. Further, on average women in the two groups are similar in age, education, health, and other factors that may affect the results. These trials are considered to be the "gold standard" studies because they yield the most reliable information.

Colorectal cancer

Cancer of lower digestive system, also known as bowel cancer.

Combination HRT

Common form of hormone replacement therapy which combines oestrogen and progesterone into a single prescription. The oestrogen combats the symptoms of the menopause, while the progesterone reduces the high risk of endometrial cancer that is present when oestrogen is used alone.

Coronary heart disease (CHD)

Results from a blockage or interruption of the heart's blood which can be due to a build up of fatty substances in the coronary arteries. If a coronary artery becomes completely blocked, it can cause a heart attack.

Deep Vein Thrombosis

Condition in which a blood clot, or thrombus, develops in a deep vein - usually in the lower leg. If the clot breaks off it can cause Venous Thromboembolism or a Pulmonary Embolism.

Dementia

The term 'dementia' is used to describe the symptoms that occur when the brain is affected by specific diseases and conditions, including Alzheimer's disease, stroke and many other rarer conditions. Symptoms of dementia include loss of memory, confusion and problems with speech and understanding.

Discovery rule

Suspends the running of statutes of limitations during periods of time in which the victim did not discover, or by the exercise of reasonable diligence could not have discovered, the injuries that would lead to his or her causes of action against the defendant/perpetrator.

Endometrial cancer

Cancer of the lining of the womb.

Estrogen

US spelling, see Oestrogen.

Food and Drug Administration (FDA)

An agency within the US Department of Health and Human Services responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation. It is also responsible for advancing public health and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

Genetic susceptibility

Predisposition to a particular disease or sensitivity to a substance due to the presence of a specific alternate form of a gene or combination thereof in an individual's genome.

Hormone replacement therapy (HRT)

A therapy that reduces the effects of the menopause by replacing hormones the body can no longer produce on its own. There are scores of HRT products and delivery can take the form of a pill, skin patch, gel or cream.

Hysterectomy

Surgery to remove the uterus and sometimes the cervix, fallopian tubes and ovaries. When the uterus and part or all of the cervix are removed, it is called a total hysterectomy. When only the uterus is removed, it is called a partial hysterectomy. The NHS estimate that in the UK 20% of women will have a hysterectomy by the time they are 55.

Medicines and Healthcare products Regulatory Agency (MHRA)

UK government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe.

Meta-analysis

A study that combines the results from several similar clinical trials that asked the same study question and applies new statistical analysis.

Menopause

The menopause is a normal change in a woman's life when menstruation stops. During menopause a woman's body slowly produces less of the hormones oestrogen and progesterone. This typically happens between the ages of 45 and 55 years old. The menopause is also triggered by the removal of the ovaries through a procedure called a hysterectomy.

Million Women Study (MWS)

The Million Women Study is a national study of women's health, involving more than one million UK women aged 50 and over. It is a collaborative project between Cancer Research UK and the National Health Service, with additional funding from the Medical Research Council, which aims to answer many outstanding questions about the factors affecting women's health in this age group. The main focus of the study relates to the effects of hormone replacement therapy use, but the large size of the study means that a very broad range of health issues can be addressed.

National Institute of Health (NIH)

Part of the US Department of Health and Human Services, it is the primary Federal agency for conducting and supporting medical research.

Oestrogen

Female hormone (US spelling, estrogen) produced by the ovaries that controls female sexual development and function.

Office of National Statistics (ONS)

The Office for National Statistics produces independent information to improve understanding of the United Kingdom's economy and society.

Osteoporosis

Disease that results in a significant decrease in bone mass with increased porosity and increased tendency to fracture.

Ovarian cancer

Cancer of the ovaries.

Progesterone

Female hormone produced by the ovaries that is important in regulating the menstrual cycle and having a successful pregnancy.

Progestins / Progestogens

Synthetic form of progesterone.

Proximate cause

An act, omission or event leading to an unbroken chain of events resulting in damage, loss or injury.

Pulmonary embolism (PE)

Occurs when a blood clot in a leg vein breaks off and travels through the body to the lungs where it becomes lodged and blocks blood flow.

Royal College of Obstetricians and Gynaecologists (RCOG)

Respected UK institution whose objective is the encouragement of the study and the advancement of the science and practice of obstetrics and gynaecology. They do this by, among other things, advising UK government, publishing guidelines and promoting research.

Stroke (cerebrovascular disease)

Arises as a result of a decreased blood supply and therefore lack of oxygen to the brain, which can cause paralysis, coma, speech problems, or dementia. Ischaemic stroke occurs when a clot blocks blood flow; haemorrhagic stroke occurs when an artery wall ruptures.

Subrogation

When an insurer, having indemnified a policyholder, assumes any legal rights the policyholder may have had in respect of that particular claim, and seeks reparation from third parties.

Testosterone

Hormone produced in small amounts in women, and can be used in hormone replacement therapy to combat loss of sex drive.

Vasculature

The system of blood vessels within the body, for example the vasculature of the heart refers to network of vessels that are distributed throughout the organ.

Venous thromboembolism (VTE)

A blood clot in a vein. The two most common manifestations of VTE are deep vein thrombosis and pulmonary embolism.

Women's Health Initiative (WHI)

The Women's Health Initiative (WHI) was a major 15-year research program to address the most common causes of death, disability and poor quality of life in postmenopausal women, namely: cardiovascular disease; cancer; and osteoporosis. It started in 1991, but the trial phase was terminated early in 2002 to protect its participants when the risks of breast cancer and cardiovascular diseases became apparent.

Women's Health Initiative Memory Study (WHIMS)

An ancillary study to the Women's Health Initiative (WHI), WHIMS was designed to determine the effects of hormone replacement therapy on the development and progression of dementia symptoms in postmenopausal women. They found that HRT provided no benefit to cognitive function and that in some women the risk of developing dementia increased.

World Health Organisation (WHO)

The directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

SOURCES OF INFORMATION

The following were useful sources of information used when drafting this report. Links are shown for ease of use and were valid at the time of publishing the report:

Office for National Statistics – Age Structure of the UK and England and Wales: Interactive SVG Charts
http://www.statistics.gov.uk/populationestimates/svg_pyramid/default.htm

NPR: Damaging News for Hormone Therapy
<http://www.npr.org/news/specials/hrt/>

The Times - Was the promotion of HRT as an 'elixir of life' a triumph of marketing over science?
<http://www.timesonline.co.uk/tol/news/uk/science/article3508126.ece>

Pulse - HRT: clarity after controversy, Dr Nick Panay
<http://www.pulsetoday.co.uk/story.asp?storycode=4115837>

Wyeth 2007 Financial report
http://library.corporate-ir.net/library/78/781/78193/items/283760/Wyeth_FR_07_lo.pdf

NHLBI, Women's Health Initiative (WHI)
<http://www.nhlbi.nih.gov/whi/>

Medicines and Healthcare products Regulatory Agency – Hormone Replacement Therapy (HRT)
[http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Hormonereplacementtherapy\(HRT\)/index.htm](http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Hormonereplacementtherapy(HRT)/index.htm)

World Health Organisation (WHO) - Global Burden of Disease Estimates
<http://www.who.int/healthinfo/bodestimates/en/index.html>

House of Commons Health Committee – The prevention of Venous Thromboembolism in Hospitalised Patients
<http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/99.pdf>

American Heart Association – Cardiovascular Disease Statistics
<http://www.americanheart.org/presenter.jhtml?identifier=4478>

Centers for Disease Control and Prevention – Lung cancer risk factors
http://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm

The Million Women Study - Patterns of use of hormone replacement therapy in one million women in Britain, 1996-2000. BJOG 2002 Dec;109(12):1319-30
<http://www.millionwomenstudy.org/publications/28/patterns-of-use-of-hormone-replacement-therapy-in-one-million-women-in-britain-1996-2000>

The Women's Health Initiative Participant Website - Health Risks and Benefits 3 Years After Stopping Randomized Treatment With Estrogen and Progestin, March 2008
http://www.whi.org/findings/ht/eplusp_3yr.php

Health-EU: The Public Health Portal of the European Union – Cardiovascular diseases
http://ec.europa.eu/health-eu/health_problems/cardiovascular_diseases/index_en.htm

British Heart Foundation - Mortality
<http://www.heartstats.org/topic.asp?id=17>

World Health Organisation – Cardiovascular Diseases, Fact sheet No. 317, February 2007,
<http://www.who.int/mediacentre/factsheets/fs317/en/index.html>

National Institute of Health - Effect of Hormone Therapy on Risk of Heart Disease May Vary by Age and Years Since Menopause, April 2007
<http://www.nih.gov/news/pr/apr2007/nhlbi-03.htm>

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