

<b>Institution: The University of Oxford</b>
<b>Unit of Assessment: 2</b>
<p data-bbox="150 327 408 356"><b>Title of case study</b></p> <p data-bbox="268 394 1326 472" style="text-align: center;"><b>HORMONE REPLACEMENT THERAPY AND CANCER RISK: THE MILLION WOMEN STUDY</b></p>
<p data-bbox="150 517 480 546"><b>Summary of the impact</b></p> <p data-bbox="150 580 1442 813">The Million Women Study of 1.3 million UK women over the age of 50, coordinated by the Cancer Epidemiology Unit at Oxford, has established the relationship between hormone replacement therapy (HRT) and breast, endometrial, and ovarian cancer, and has had a dramatic effect on HRT prescription patterns and prescription guidelines worldwide. This has had a major impact on women's health. Prior to the study, one third of UK women aged 50-64 were using HRT. The marked decline in HRT use following publication of the study's findings has led to a reduction in the incidence of breast cancer among menopausal women.</p>
<p data-bbox="150 853 475 882"><b>Underpinning research</b></p> <p data-bbox="150 920 1442 1084">Clinicians have questioned the health impacts of hormone replacement therapy (HRT) for decades. Although originally touted as a wonder drug benefiting health, vitality and femininity, HRT has been plagued by fears of its relationship to cancer since the 1950s. At the turn of the 21<sup>st</sup> Century these fears were supported by a number of studies showing the correlation between HRT and cancer, in particularly the Women's Health Initiative (WHI) study, which took place in the United States.</p> <p data-bbox="150 1122 1366 1218">Initially dismissed in the United Kingdom, due to the WHI study not being based on European women's health, the need for a similar epidemiological study to reflect the risk factors of HRT among women in Europe became a high priority.</p> <p data-bbox="150 1256 1410 1384">Setting out to understand the health impacts of HRT from a European perspective, a team coordinated by Professor Dame Valerie Beral of the University of Oxford's, Cancer Epidemiology Unit, began recruiting a large number of UK women to investigate how reproductive history can affect women's health – focusing particularly on hormone replacement therapy.</p> <p data-bbox="150 1422 1422 1518">The Million Women Study, launched in 1997, has since recruited 1.3 million UK women over the age of 50, through NHS breast screening centres. It is the largest study of its kind in the world [1], with one in four UK women in the target age group participating.</p> <p data-bbox="150 1556 1345 1621">Results of the study have been published in more than 50 papers since 1998 [2], primarily examining the effect of HRT on the development of breast, endometrial and ovarian cancer.</p> <p data-bbox="150 1659 1430 1890"><u>Breast Cancer</u>: In a landmark paper published in 2003, the Million Women Study showed that women taking HRT were at an increased risk of developing breast cancer, with an estimated 20,000 UK women aged 50–64 having potentially developed the disease due to HRT use [3]. The study also showed that the risk of side effects increased the longer a woman used HRT, but dropped to a normal level five years after the use of HRT had ceased. Analyses in the Million Women Study have also demonstrated that the effects of HRT vary considerably by pattern of use and tumour subtype [4].</p> <p data-bbox="150 1928 1437 2054"><u>Endometrial Cancer</u>: In 2005 the Million Women Study confirmed that post-menopausal women who have not had a hysterectomy (and are taking oestrogen-only HRT), are at an increased risk of endometrial cancer [5]. The study also showed that the risk of endometrial cancer increases in women who take the HRT drug tibolone, but may be reduced in women taking combined</p>

## Impact case study (REF3b)

oestrogen-progestogen HRT. Interestingly, they also found that these effects were dependent on a woman's body mass index, with cancer risk being greater in thinner women than in those who were obese [5], as had been observed for breast cancer risk [3].

**Ovarian Cancer:** Results of the Million Women Study published in 2007 showed that women taking HRT were at a slightly higher risk of ovarian cancer [6]. The study analysing 948,576 post-menopausal women over five years found that for every 1,000 women taking HRT, 2.6 developed ovarian cancer, compared to 2.2 in those not taking HRT [6].

## References to the research

[1]. Million Women Study. *cancerscreening.nhs.uk* at <http://www.cancerscreening.nhs.uk/breastscreen/research-million-women-study.html>. [Accessed 6/09/13]. **NHS website referring to the Million Women Study as the largest study of its kind in the world.**

[2]. The Million Women Study: Million Women Study. *millionwomenstudy.org* at <http://www.millionwomenstudy.org/publications/> [Accessed 6/09/13]. **The Million Women Study website showing the number of publications that have resulted from the Million Women Study.**

[3]. Beral, V., Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* **362**, 419–427 (2003). PubMed ID: 12927427. **Paper on the relationship between breast cancer and HRT.**

[4]. Beral, V., Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst.* **103**, 296-305 (2011). PubMed ID: 21278356. **Paper on the relationship between breast cancer and HRT by pattern of use and tumour subtype.**

[5]. Beral, V., Million Women Study Collaborators. Endometrial cancer hormone- replacement therapy in the Million Women Study. *Lancet* **365**, 1543–1551 (2005). PubMed ID: 15866308. **Paper on the relationship between endometrial cancer and HRT.**

[6]. Beral, V., Million Women Study Collaborators, Bull, D., Green, J. & Reeves, G. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* **369**, 1703–1710 (2007). PubMed ID: 17512855. **Paper on the relationship between ovarian cancer and HRT.**

This research was funded by Cancer Research UK, the NHS Breast Screening Programme and the UK Medical Research Council.

## Details of the impact

Results from the University of Oxford's Million Women Study, have changed attitudes towards HRT dramatically, leading to significant changes in public policy and HRT use around the world. This research has also led to significant reductions in breast cancer incidence amongst menopausal women.

Public Policy

Results from the Million Women Study have influenced a number of European health agency guidelines, which now recommend that women at a high risk of breast cancer consider alternative options to HRT. These agencies include the Royal College of Obstetricians and Gynaecologists [A], the Medicines and Healthcare products Regulatory Agency [B], and the European Medicines Agency [C].

## Impact case study (REF3b)

Culture and Behaviour

Since publication, the Million Women Study has been presented to the public at length both in print and online – from articles in the *New York Times* and *Daily Telegraph* to women's health blogs and cancer charity websites around the world.

This far-reaching public awareness of the study and its findings led to significant behavioural changes, predominately resulting in the swift decline of HRT prescriptions throughout Europe and the US from 2003. In stark contrast to the increase in HRT prescriptions between 1991 and 1996, which remained stable through to 2001, sales of HRT fell by 50% between 2002 and 2005 following the publication of the WHI trial and the Million Women Study [D]. Recent studies demonstrate the continuing impact of this research on behaviour in terms of continued reduced HRT use [E, F].

One such study published in 2010 in Belgium (a country known to have one of the highest incidences of breast cancer in Europe), shows that the proportion of women aged 50-69 years using HRT in Flanders went from a 20% peak in 2001, to just 8% in 2008. The study also showed a decrease in breast cancer incidence [G].

Health

Due to the substantial decline in the use of HRT in many countries, the incidence of breast cancer has markedly decreased in women between the ages of 45 and 64. Declines in the rate of breast cancer have been strongest for women between the age of 50 and 60 years, with rates which were previously on the incline dropping by 0.8% a year [H, I]. More recent data [E, F, I], which were published between 2010 and 2012, show that lower levels of HRT use and breast cancer incidence subsequent to the steep decline in HRT use, which followed the publication of the Million Women Study, have continued into the REF assessment period of 2008 – 2013. Breast cancer incidence in Great Britain among women aged 50 to 64 peaked in 2004 and then showed a rapid decline over three years, with the lower rates then persisting through to at least 2010 (the most recently available incidence data) and being partly attributed to the reduction in HRT use in this age group [I]. Similarly, a report assessing breast cancer incidence in Belgium up to the end of 2008 showed a significant drop in breast cancer incidence, which was attributed to the significant decrease in HRT use in Belgium during and leading up to 2008 [F].

**Sources to corroborate the impact**

[A]. Whitehead, M. I. RCOG study group on menopause and HRT RCOG recommendations on hormone replacement therapy. *Lancet* 365, 749 (2005). PubMed ID: 15733708.

***Paper making Royal College of Obstetricians and Gynaecologists recommendations on HRT use for menopausal women, which although published in 2005 has not been superseded.***

[B]. Further advice on safety of hormone replacement therapy (HRT), at <http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON002044> [Accessed 6/09/13].

***Recommendations from the Medicines and Healthcare products Regulatory Agency (UK) on HRT use, which refers directly to the Million Women Study.***

[C]. European Medicines Agency. [ema.europa.eu](http://www.ema.europa.eu) at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003348.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003348.pdf) [Accessed 29/09/13]. ***Recommendations from the European Medicines Agency on HRT use, published in 2005 but remaining in force and hence achieving impact during the assessment period. The Million Women Study is cited as one of the main sources of evidence (see page 9).***

[D]. Watson, J., Wise, L. & Green, J. Prescribing of hormone therapy for menopause, tibolone, and bisphosphonates in women in the UK between 1991 and 2005. *Eur. J. Clin. Pharmacol.* 63, 843–849 (2007). PubMed ID: 17598097. **Paper showing drop in HRT prescription rates following the publication of Million Women Studies.**

[E]. Renard, F. et al. Decline in breast cancer incidence in the Flemish region of Belgium after a decline in hormonal replacement therapy. *Ann. Oncol.* 21, 2356–2360 (2010). PubMed ID: 20439342. **Paper on the decline in breast cancer rates following the drop in HRT use in Belgium.**

[F]. Antoine, C., Ameye, L., Paesmans, M. & Rozenberg, S. Update of the evolution of breast cancer incidence in relation to hormone replacement therapy use in Belgium. *Maturitas* 72, 317–323 (2012). PubMed ID: 22627077. **Recent study on the decline in breast cancer rates following the drop in HRT use in Belgium.**

[G]. Parkin, D. M. Is the recent fall in incidence of post-menopausal breast cancer in UK related to changes in use of hormone replacement therapy? *Eur. J. Cancer* 45, 1649–1653 (2009). PubMed ID: 19217279. **Paper showing the declines in the rate of breast cancer since 1999.**

[H]. Verkooijen, H. M., Bouchardy, C., Vinh-Hung, V., Rapiti, E. & Hartman, M. The incidence of breast cancer and changes in the use of hormone replacement therapy: a review of the evidence. *Maturitas* 64, 80–85 (2009). PubMed ID: 19709827. **Paper reporting behavioral changes in HRT use and the subsequent health outcomes.**

[I]. Cancer Research UK Breast cancer statistics. [cancerresearchuk.org/cancer-info](http://www.cancerresearchuk.org/cancer-info)  
<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/uk-breast-cancer-incidence-statistics> [Accessed 6/09/13]. **Cancer Research UK information sheet reporting breast cancer incidence data and directly citing the Million Women Study research on HRT and breast cancer (see Figure 1.4 and subsequent text, citing reference 11).**