Age-specific incidence of important conditions in women (rate/1000/year)
Thanks to the audience for coming. The title was a little bit dull, “The Million Women Study”, but what I am really going to talk about, which is important, is one of the reasons the study was set up was to look at questions, look at behaviours, normal sorts of behaviours, what women do, to ask the question: what can women do to stay healthy? Every day, there is not just one article or something in the newspaper or on the internet; there are usually lots and lots saying: if you run, you will not get dementia; if you drink orange juice, you will not get breast cancer, etc. etc. The interesting thing is that the public have quite a strong sense that a lot of this stuff probably is not true. It is interesting how people do not disregard a lot of things that they read, and rightly so, because often people do quite small studies and look at some little sub-group and find something that they think is very newsworthy and rather push that, and what I think I have tried to do in my life is to try and really be real about things and really to just understand and be really clear when one says...what was said today, and is right actually: even if you lose a little bit of weight, it is good for you, and that is true. So I am going to talk about things that we really know about, and the reason we know about it is combinations based on large numbers, reliable data, not nit-picking through things to see if we can find something that might sound very interesting in the short term. So, that is really what I am going to emphasise, and that is really why I started the Million Women Study, and I will talk about that – I will get there.

I am going to be looking at questions such as what are the effects on health of major lifestyles? And I am going to talk about lifestyle factors that you can potentially modify. Although it is not a lifestyle factor, one of the things we found is that the taller you are, the more likely you are to get cancer. Now, that is interesting in a biological way, but you cannot do anything about your height, so it is not in the same...and I am not going to talk about things that are not modifiable, or potentially modifiable here.

Now, you will see that it is very important to know the effects of some lifestyle factors, say smoking. I am going to talk about the pill, hormone replacement therapy, obesity, adiposity, physical activity, alcohol, diet, smoking – these are things you hear about all the time. It is really important to know whether effects are persistent or not because you only, for example, take the pill – women only take the pill for a short part of their life, when they are in their twenties, thirties, usually. HRT, women take at a different age. So, you have to ask: does it matter if these drugs, if they have an effect, does it persist or not? So I am going to talk about that a bit, and I am also going to just talk about the magnitude of effects – what are the big things and what are the little things? I am going to talk mostly about things that you hear about on the news etc.

I’m going to start with talking about conditions that are important, that people know about, that everyone in the audience here will know about, things that you read about – heart disease, hip fracture, which is a manifestation of osteoporosis, breast cancer, and venous thrombosis. The first thing that is really important to understand about all these conditions is that they each have a very characteristic age pattern. I will start with venous thrombosis, or thrombosis, often people call it, which you all know is associated with the pill and I will talk about it in a minute, but you see, for women in their twenties and thirties, thrombosis in the legs that can cause a pulmonary embolism – it is a clot that can occur in the legs and actually go into the lungs and people can die from it. You see, for women in their twenties and thirties, it is more common than breast cancer, heart disease and all sorts of other things, which is why, in a way, there has been so much emphasis on thrombosis and clots and women on the pill. It is because it, in young women, it does occur, whereas heart disease hardly occurs at all, and breast cancer really does not pick up until about the forties, but breast cancer does not increase as you get past fifties. Breast cancer is the most common – women in their forties and fifties - condition, but by the time you get to sixties and seventies, heart disease takes over. So, all these things are very important when you think about specific effects of different things and what you should be thinking about in terms of disease and what can happen, and as I said, and also what is persistent or not.

Now, you can see how hip fracture in yellowish goes up very rapidly with age, much more rapidly than say heart disease. Heart disease is going up quite a lot, but then hip fracture, osteoporosis, goes up much faster and
overtakes heart disease. And dementia, which we are starting to work on and it is very important, dementia is pretty well unknown before about age 70, not entirely, and it just takes off and overtakes everything, but really sort of late-80s, 90s, so that issues to do with dementia become important later. But one has to ask, is something – these sorts of questions: is there something you can do in your 50s that will prevent dementia, or is it something you should be doing in your 70s? Are there persistent effects? It is those sorts of questions. So, age is really important in trying to understand the effects of many of these exposures.

I have already mentioned the pill and the fact that we all, again, read in the paper, clots, and that one pill is worse than the other pill and so forth, but it is right, the thing that one should be concerned about for the pill is really blood clots because that is what is more common in younger women, unless there is a persistent effect of something that is adverse.

But you see, hormone replacement therapy, as people usually call it, although the word “replacement” has gone now because I think it was always a silly word and it does not replace anything – well, it might, but it is an idea that was pushed, and this idea that it was replacing things that went wrong after the menopause is not necessarily right, but anyway, I am using HRT because people know the words.

You can see that, at the age when women take HRT, which is in their fifties and sixties, it is breast cancer, particularly women in their fifties, and heart disease are the biggest issues, so I want you to think about these things. As I have said disease rates vary by age. So do lifestyle factors and behaviours vary by age, and one has to ask what are the effects and whether they persist or not because that is really important in trying to understand the short term and long term effects.

I am going to start with the pill because actually this is how my career started and maybe, I do not know whether you in the audience are so interested in the pill, but there was a time – the pill came out in the ’60s and it is, although people forget, it is the most widely used drug. 600 million women have used it, and there are 120 million currently using it, and interestingly now, there are far more women in sort of mid and low income countries using the pill than in high income countries. But if we think about high income countries today, I do not know whether this will surprise you or not but it sort of surprises me, that women, if you look at women in their 60s now in the UK, about 80% have ever used the pill, and for an average of seven years, so it is quite a long time, and women who are 90 today, 30% have used the pill for an average of about five years. So, there has really been not only “Is it so widely used?” but now really women of all ages have used it and so there are questions again. And there has been a massive amount of research, more than probably on any other drug, I will call it for these purposes, and we do really know a lot about it.

The interesting thing is, if you go back in the ’60s and ’70s, the first adverse effects that were reported were all vascular, things to do with the circulation. The first, in 1961, a year after the pill came out, there were already reports in medical journals of people, young people on the pill with venous thrombosis or blood clots which were unexpected. By 1962, there were 26 cases reported to the FDA, the Food & Drug Administration in the US, and so already, within years of the pill being made available, there were already reports of adverse effects. Soon after, in ’62, the first report of a stroke, and ’64, the first report of coronary heart disease.

Now, what all the studies have shown, and there was a huge amount of work done in the ’70s, late-’60s and ’70s really, that showed that there is a two to four fold increase in the risk of blood clots, maybe not so large, but not too different for stroke and heart disease. But the important thing is this line down the bottom, that these effects are reversible. When women stop taking the pill, there is no persistent risk, so it goes away. So, while there are risks, they are reversible and so, you have already seen but I will come back to it, venous thrombosis is commonish, but pretty rare when you compare it with other ages, but the most common condition in women who take the pill, as a background rate, and people who are not on the pill but at the age groups that take the pill, is venous thrombosis. So, that is what should be the main concern and it still is.

But you see, the interesting thing is, when the pill was first marketed, and there had been a couple of studies, there had been some little – well, I would call them little, but they called them large then – studies in Puerto Rico of women given the pill. There was a bit of a worry that there may be cancer risks, and actually, cancer, when the pill was first marketed, it was cancer people were worried about and not vascular disease. But in the ’60s and ’90s, the emphasis did turn to cancer and there were a huge controversy. Again, some of you might remember – it is interesting just looking back in time. I cannot think of an equivalent controversy at the moment.
So, there was a huge furore in the late-1980s about whether the pill caused breast cancer, and some people said it did and some people said it did not, and there were big arguments, big scientific arguments. I am just trying to think of an equivalent thing today and I cannot immediately think of how heated it was. There was something in the paper all the time, someone claiming one thing and the other thing.

I went to Oxford at the end of the ‘80s really, in 1989, and it was really clear that someone had to sort out what was going on by actually bringing all the warring parties, you could call them, together, and just asking everyone to put in their original data and to merge it and to see what was going on. We set up this collaborative group on hormonal factors in breast cancer, and we set up in Oxford and we have meetings every five years – it still continues. The first results were published in 1996. Now, I am going to be showing probably more detailed results than you need to see, but just you can listen to me if you do not want to look at the figures. But what we found was really unexpected. Time is on this axis here, and this is like comparison with never-users of oral contraceptives. If there were points down here where main pill users did better than never-users, up there, they did worse. We found that people who were taking the pill had a relative risk of 1.2, which means about a 20% increased risk of breast cancer when they were taking it, and this is after years of stopping, and by ten years after stopping, this risk had gone away, so that the worst – and this was very unexpected because people generally think of cancer being caused something you do now and it has its effect a long time later, but what we found – but there is actually not as much reason to back up the idea that cancer is caused by long term exposures to things. Although it is a commonly held view, but it is not true, and a lot of the work that we have done has shown it is not true. So, very unexpectedly, we found, when you put the worldwide evidence together – this is from about 50 studies, about 50,000 women with breast cancer – we found that there was an increased risk, 20% increased risk, while people were taking it, and a few years after stopping, that had gone after about ten years. It was very clear and all the divergent studies all fit in once the basic pattern had been clarified, and so the studies were not disagreeing. It was just that people who were looking at older women, who had stopped the pill long ago, were saying there was not an increase, and people who were looking at younger women who were still on the pill were saying there was an increase, but there was no difference across studies. That was really a terribly important finding, really clear, and that this excess risk of breast cancer is reversible, and you now never, ever hear in the press, after we published this in ‘96, there’s no discussion anymore about the pill and breast cancer. It is widely accepted that is what it is.

We have also done the same thing for cancers of the ovary and endometrium, and I think what I said before is, if you look down here, so this is never-users of the pill, actually, cancer of the ovary is reduced in pill-takers, as is cancer of the endometrium, the lining of the uterus. So that, contrary to breast cancer, the other sort of cancers in women that are hormonal, related to hormones obviously, to reproduction or organs of reproduction, the pill actually protects. This is the length that the pill has been used. The longer people have taken the pill, the greater the protection. You cannot see this, but these are different lines on when people stop taking the pill, and essentially, quite different from breast cancer, the pill protects against ovary cancer and cancer of the endometrium, or the lining of the womb, and it’s a persistent effect. Now, no one could have guessed this. We did the same thing of bringing together the worldwide evidence, and until you have all the data together and you make sure, and again, there was not any variation between studies, and there was not variation between some sub-groups. Some published…you hear, if you eat cereal and you take the pill, you are more likely to get this or something, but once you bring all the data together and you look inside, a lot of these sort of little sub-groups, effects that seemed sensational at the time, go away. So, this is what we found, and I am leading into the Million Women Study now, but you see, 50 years of research has taught us about the pill, and really a huge amount of research.

As I have already said, while the pill is being used, there is an increased incidence of vascular disease and also breast cancer, but these effects are reversible – there is no persistent effect. And because most of the serious illnesses in women, like breast cancer, cancer of the ovary, heart attack and everything, are rare in women in their 20s and 30s, except perhaps venous thrombosis that we have talked about, the numbers who have adverse pill-associated illness is very small. I mean, I have not gone through the absolute rates, but this is like one in 100,000 per year or one in – very, very small risks. So, although there is an increase in conditions that we have talked about, the excess risks, it is unusual to suffer from these side-effects.

In the long term, what we have is a persistent decrease in cancer of the ovary and the womb, and where we are now is that, in the long term, women who have taken the pill, they have a net reduction in cancer incidence. So, actually, and there is no one that pushes this idea very strongly, but really, I mean, women who have taken the pill are at a reduced, in terms of their cumulative risk, a reduced risk of cancer, and it really is something that one can say quite, I mean, it is true. And, you know, there is so much “What can we do for cancer prevention?” but it is interesting that people are very nervous of saying “Take the pill” – it is very interesting, is it not?
Anyway, now, HRT. When we were bringing together all the data I showed you on the pill and breast cancer, it was really clear that HRT, there was quite a hazard of breast cancer in people on HRT. Most of the data – this, remember, was in the sort of early-’90s – most of the data at that time came from the US. There was not so much use of HRT in the UK at the time. The sort of HRT being used in the UK was not the same as in the US, and also it was clear just from what was going on that HRT use was rocketing in women in the UK. So, we decided that we really needed to do a study looking at the association between HRT and breast cancer because, as you can see, most of the users of HRT were women after the menopause in their 50s and it really was breast cancer that was looking quite worrisome. There had been a trial looking at heart disease as well, women in the US, and I will talk about that, but they are the two conditions I am going to talk about as far as HRT is concerned.

The women who were screened for breast cancer at that time were women in their fifties and sixties and we asked the screening centres – and I am going to say a bit about screening in a minute, but there are about 100 divisions in England, Scotland and Wales, which 100 – there used to be, I think, not regional health, some health authorities, and in every one of those regions, there was a centre where the spots are, but not all of them have got spots. There were about 100 centres that ran breast screening through the country, responsible for each of those areas, and the ones with the dots in them are the ones that took part. These ones did not, some areas. So, we asked each of the centres separately, and if they agreed, they put a study questionnaire in the envelope when women were invited for screening, and women were asked to fill out the questionnaire if they wanted to, they could – we were interested in HRT and breast cancer, but women’s health in general, and they could fill out a questionnaire, and it was handed in separately from the screening programme because we had to show that we were not in any way changing the way the screening programme ran because it was a very efficient organisation and we did not want to change that. So, over about a five year period, ’96 to 2001, we managed to recruit 1.3 million women who were 50-64 – that was the age that was screened then – which was about one in four of all women in the UK actually who were aged 50-60 at the time, and it was about one in two in the areas that we covered.

I am quite sure that some of you – if it is one in four women who are aged 50-64 at the time, I am quite sure some of you in the audience are part of that and we send you questionnaires from time to time, and it is very hard to say thank you in person to so many people, so I will say in person to you, and if this is recorded, I will say it to people who look at this over the internet as well, the study obviously would not exist without you, and with the questions. I think people often think how can these rather simple questions really help, but we do a lot of repeat – you might have got the same questionnaire again, where we ask the same question later and look at how well things agree, and actually, I think you would be surprised because, I think when you fill these questions in, you think, oh, I am just saying off the top of my head, but people tend to say the same thing over and over again. And we have got blood and we do all sorts of tests, so basically, the answers are much more reliable. It is more important to give a rough answer than to leave these blank if you are not sure and we always say that.

When women were recruited in the study, they were 56 on average. Now, 14 years later, they are 70, and that is why I think I said that we are starting to get interested and really want to do work – I started with the pill and HRT. We are going to start doing serious work on dementia next, but I am not talking about dementia now because women are just starting to develop dementia.

So, that is the Million Women Study, and we set out to look at breast cancer and hormone replacement therapy. Now, these are actually real rates. This is, in 1,000 women over a five year period, and it shows you how common breast cancer is, so much more common than cancer of the ovaries...still, it does. Breast cancer in never-users is so much more common than the other two cancers. So, if you have even a small effect on breast cancer in terms of how common it is, it affects large numbers of people.

I had said before that the type of HRT used by women in the UK was not the same as in the US. In the US, most of the HRT users just had oestrogens in them, but in the UK, what had been shown before was that HRT containing oestrogens only increased the risk of cancer of the womb, cancer of the endometrium, which was known about. So, in the UK, much more than the States, they said anyone who has got a womb should be given it. Instead of saying something else but they added something else – instead of just saying, “Well, maybe you should not take it,” or something, they said, well, let us put in another hormone, so you have got oestrogen plus progestagen, which, as you can see, women who are taking oestrogen plus progestagen – and this is much more used in Europe and the UK than in the US – so women, it is true that women who took oestrogen plus progestagen did not have an increase in cancer of the endometrium, whereas they did if they had oestrogen only. But little did the gynaecologists know that what they were doing by adding progestagen is increasing the risks of breast cancer really quite substantially. Ovary cancer, although the numbers look very small, is slightly increased in pill users, but it is small. You can really see that, when you put all the sort of hormone-related...
cancers together, it is breast cancer that predominates. And as I was saying, if you put them all together, in five years, about 20 women in a 1,000, so two in a 100, will get one of these cancers, over a five year period - this is women in their 50s and early-60s. So, it is not a small number, 2%, two in 100. If you take oestrogen plus progestagen, it goes up to over three, so it becomes 3% instead of 2%. Now, that means that one woman in 100 over a five year period, for every 100 taking HRT, one more is getting breast cancer. It is quite a big number. It is not a small number. As I said, the pill related things were in the one in 100,000. This is one in 100, much bigger effects, and now studies in Europe have generally found exactly the same. As I said, in the States, this oestrogen-only tends to be used and it is not half as bad as adding the progestagen.

The other thing that we found, just as with the pill, that the excess risk, and this is like in the same format as I showed for the pill, that although there is an increase, much bigger, about 20% increase for the pill, current users of the pill, it is about a 70% increase, but again, after stopping, and here it seemed like four or five years after stopping, the risks were the same as never-users. So, the good news, and the important news, is it is reversible. The effects of HRT on breast cancer are reversible. So, although there is an increased risk, as with the pill, it seems to be a short-term effect.

Now, I am not going to talk about coronary. We are just analysing that now and these are results from the randomised trials that were done in America, as I said, at the same time about as we started the Million Women Study.

Basically, HRT use was increasing very rapidly during the ‘90s because it was widely said that women who took HRT, their risk of heart disease was reduced and that they would live longer and so forth, and all sorts of claims. But the randomised trials – I will not go through and explain this, but basically, it did not matter whether they were taking oestrogen-only or oestrogen plus progestagen, there was really little evidence – there was certainly no decrease in risk, and not much to say there was an increase. The MHRA, which is like our FDA equivalent here, they said there is no evidence, because some people argue, if you start when you are very young, it is beneficial, but there is really not much evidence to say it is beneficial. Anyway, so we published on breast cancer and the trials in the US published about the same time around – the trials in the US published 2002, and we published our results on breast cancer in 2003.

You can see this extraordinary thing that happened in the UK. In a very short – since about the mid-‘80s, use of HRT went from almost no one to 2.5 million users in the UK, but with the results particularly of the trial showing there was not a benefit of cardiovascular disease, and possibly, they said possible decrease, and others showing increase in breast cancer, there has been this rapid decline. It has not gone away completely, and actually, we have got some even more recent figures, and it looks as if it is levelling off, so it has not gone down at all. So, there is still about a million users of HRT in the country, but it is interesting to see how rapidly and how the public actually realised this was real. And, I said before that a lot of the findings that you hear about in the media and so forth, people do not react to, but they reacted to this very well, and I think that people who read the papers, listen to things, seem to know the difference between reality and what is real and what is hype, and this was real. It is particularly breast cancer that is the problem, and it is just interesting to see how rapidly use fell, and also showing that it was not the elixir of youth or whatever it was sold as.

What has been published since then – and I said it is reversible, the effects – the drop in HRT use, this is a bit complicated, you do not have to see this. This is data from the States, where use of HRT fell very quickly, and breast cancer incidence fell, and it was particularly breast cancers that are responsive, that are called oestrogen, with oestrogen receptors, and that has been in a dozen countries now, so that, following this drop in use of HRT, breast cancer rates have dropped slightly in women in their 50s and 60s.

Interestingly enough, I will just show this and not say anything about it, but coincident with the drop in HRT use, in the UK, and I presume - or this is data for England, but I presume it is true everywhere, many other places, there has been an increase in prescription of drugs called bisphosphonates. I should have said actually, that HRT is very good for the bones and that there is a reduction in fractures and osteoporosis, but it is while women are taking HRT, but if you remember, it was women in their 80s who get osteoporosis, sort of late-70s and 80s, osteoporosis and fractures and problems with osteoporosis, and taking HRT when you’re 50 is not going to help osteoporosis when you are in your 70s and 80s. So, what has happened is these drugs called bisphosphonates have just taken over. I mean, it is very interesting how doctors want to prescribe something else. If you are not prescribing HRT, we will try something else, and I will tell you, we know almost nothing about what bisphosphonates do, and that is another thing that we are planning to do in the future. But they have taken over
I just want to say, although I have not done work on this, but we did recruit through the screening centres, and that is why there has been a lot of fuss about in the media lately – you have probably read that, and actually, I know from attendance figures that people have pretty well ignored all the fuss because there has been a lobby saying that breast screening does not work and you should not go and it does more harm than good. Well, it is just not true. There was a big review – and there have been a dozen trials. This is just to show you that there have been different trials, in the USA, Sweden, UK, Canada, Finland, all these trials randomising people screened or not have shown benefits. There has been a lot in the media about that, and finally the Government set-up an independent review, and they said, yes, it does save lives, there have been 1,400 fewer deaths from breast cancer in England every year because of screening. I just want to say – it is not my research – but it is not a behaviour either, but screening does work and does reduce deaths from breast cancer, and there’s not much we can do otherwise about breast cancer, so it is important.

If people have very bad menopausal symptoms, and that is what the MHRA, I was going to say, the FDA-equivalent, says, if you want to, you should take HRT for as short a time as possible for severe, for real symptoms. But there is a bit of a movement now with the drug company and people who made a nice living out of HRT beginning to try and say, oh, all the evidence was wrong, ten years ago, ignore everything that has happened and go back to HRT. There is quite a push. It is interesting, all these lobbies, as I said, there has been an anti-screening lobby, there is a growing pro-HRT lobby. But, as I say, I think people are very sensitive to all these things.

As I said, we heard today’s news event is, if you lose a little bit of weight, it is good, and the answer is that is right. Now, all of this is a bit too much. I am not going to go through this in detail, because the study is so big, out of the 1.3 million, there are about 100,000 women who have developed cancer of some sort, and so we have a lot of statistical power where we can just see exactly what does and this is a 10 unit increase in BMI. It is like being from normal weight to obese. So, if you go from normalish weight to obese, what happens to cancer risks? We have taken the 18 most common cancers here. I am not going to go through them all. But if there is a square on this side, it means obesity is bad for you; if there is a square on this side, it means it is good for you. Now, for most of the cancers, and particularly the endometrium, which I have talked about a lot, cancer of the womb, the difference between a normal weight woman and someone who is obese, the obese woman is 2.8, almost three times as likely to get endometrial cancer, and so forth and so forth. I am not going to go through them all. Smaller effects for some things, but nine out of the 18, down to here, there is all significant increases with obesity. Some of the ones, there is no effect with obesity, and two really, cancer of the lung and squamous cell, one of the cancers of the throat, there is a decreased risk. But mostly, being obese is not good for cancer.

It is much worse for other things though. This is for non-cancer risks. We took the 25 most common conditions women are admitted to hospital for, and for 21 out of the 25, being obese was a bad thing, topped by, as you all know, diabetes, but the second, again which people do not know so well, is knee replacements. The magnitude of the effect of obesity is almost as bad as for diabetes. Women who are obese are much more likely to have to have a knee replacement, have knee problems. Venous thrombosis is quite high, and gallbladder disease, carpal tunnel syndrome, atrial fibrillation, hip replacements, these things are all more common. Ischaemic heart disease, down here, which you hear about. I have not shown all the list, but again, obesity is bad for most things. It is good for just a few things, a very small number of things.

People who are morbidly obese are eight times more likely to get endometrial cancer of the womb than normal weight women. But the next slide...so this just shows you...and there is a linear relationship: the more obese you are, the greater the risk.

The next slide is a bit complicated and I am just going to tell you what it shows because it is a little bit hard and I am sorry about this. This shows what your body size was – we asked people and we have been able to validate and show that this was true when we have got actual measurements of people. People who were thin, and average, or plump, when they were ten, and this is what they were when they were ten, and these things are what their BMI is now, what they are now, and this is saying women who are not overweight, who are normal weight now, in their 50s and 60s, it did not really matter – their endometrial cancer risk did not really matter, it did not matter whether they were thin, average or plump when they were ten. So people who are obese now, it did not matter if they were thin, average or plump when they were ten, and similarly people who are in what is called the overweight group, did not matter if they were thin, average or plump. So, what this is saying, and
really important, is that it is what you weight now that is important. There does not seem to be a persistent
effect from the past. There is a persistent effect, you can say, that most people who were plump when they
were young end up plump when they are older, but if you look within strata and hold these things constant, it
looks as if there is not much effect on endometrial cancer and on the other cancers we have looked at what you
were when you were younger. And this is, you know, the extremes are here...like if you are lean at 10 and obese
at 60, you are the same as if you were plump at 10 and obese at 60, and these are people who were plump at
10 but lean at 60 and they are the same. So, the extension of this is it is what you are now that matters. And, in
a way, it is also implying these things are reversible. What happens to you at a certain age, if you get to 60, is
what you are at 60 that matters, not what you were when you were 10. So, it is a bit of a similar sort of message
to the pill or HRT, that really, it is what you do now that matters, and so that is why what I said was right, what
was in the news today, losing some weight now can help you because it is what you are now that is important,
and that, I think, should be seen as quite a relief to people, that you can still change – if you change your
behaviour now, if you change your weight now, it is worthwhile.

Physical activity matters, but it matters in different ways for different conditions. We have just looked at
fractures, for example. These are people who were active. For hip fracture, the more active you were when you
filled out the questionnaire, the more active you were, and we then followed people to see if they had hip
fractures. Being active was very good for hip fractures. But interestingly enough, for ankle fractures, and for
wrist fractures too, if anything, there was no effect, or even a slight increase, and I think that, again, if you are
more active, you can fall over more, but the very serious hip fractures, you are protected against, presumably,
for all sorts of reasons. But it is just to say that it is not always the same for every condition, and not all
fractures are the same.

Now, we have just got this result, which we have not published yet, and it is a bit curious, but we have also
looked at physical activity and vascular disease. This is heart disease, this is stroke, and this is blood clots,
venous thromboembolism, and this is quite curious in that people who are pretty well inactive – and this is
strenuous activity, so they rarely or never do anything, compared with them, if you do some sort of activity
once, up to once a week, two to three times a week, it is a very good thing, as one has heard, and that is true,
but we do find this odd thing here, that the very active, being active more than three times a week, doing
activities, there seems to be an increase in this. As I said, it is not published yet – curious and it may fit with, you
often hear about people being very, very active and then having some catastrophic vascular event, and that
might be what our data is showing too. But generally, for most people, physical activity is a good thing for heart
disease and stroke, but maybe one should not overdo it.

Alcohol and diet. Now, I am just going to show you this. It is very important because there is a lot of talk about
alcohol and cirrhosis. I think mortality from most conditions in the UK is falling, particularly from vascular
disease, is falling very rapidly. Expectation of life is increasing very fast. But one of the few conditions where the
incidence rates are really going up quite rapidly is cirrhosis of the liver, and it is not only alcohol. Women do not
drink very much. The average, for women in general, is less than one drink a day. But for women who drink
about one drink a day, they have got a significantly greater risk of cirrhosis, so one drink a day is enough to do
this. Once you get to almost three, you can see, there are very big risks – they go up quite fast. But there is
also a difference between non-obese and obese. At every level of alcohol consumption, obese people have
higher rates of cirrhosis, and probably the reason cirrhosis is going up is a combination of people drinking more
and being more obese, because rates are really going up very fast, and as I say, women do not drink much, but
even at the very small levels, one drink a day, on average, two drinks a day, you can see the effects.

Now, I am going to say the same, alcohol also, if you do the same – I showed you this long plot, the different
sorts of cancers, for obesity. If you look at alcohol, alcohol affects some cancers. It is not as great an effect as
obesity, but the one that is really important, particularly for women, is it does increase breast cancer risk, and so
it is 12% for 10g. This is grams a day I am talking about, not obesity - this is for one drink a day, on average. So,
it is about a 12% increase for every drink. So compared with none, women who drink nothing, women who drink
one drink a day on average have about a 12% higher risk of breast cancer, and if they do two drinks a day, it is
24 and so forth. Again, it is because breast cancer is really common in women this is quite an important result.
But you will see, which others have reported too, that some cancers are reduced with alcohol, so it is not a
totally simple picture. The size of these squares tells you something about how common the diseases are, and
breast cancer really dominates the picture. We also found, I mean, as others have found, but basically, the
cancers that are affected by alcohol are, not surprisingly, ones of the mouth, the larynx, the pharynx, the
esophagus, the gullet, and the liver. It is not surprising, the ones that are increased, and most of the other
cancers are not increased.
Oh, and just to say that it does not matter – this just shows people who just drink only wine, or other mixtures. It does not matter. It is the same – it does not matter where the alcohol comes from, the effects are the same.

Diet and fibre. I am just going to show you one slide that we have got - diverticular disease of the bowel is a condition where, in the colon, you get little pockets that can get infected and cause all sorts of abdominal problems. We really found a strong association, the more fibre you ate, the less likely that was to be. But we are actually having trouble finding, or reproducing what other people have found about diet, so that, if I just say, for the moment, that much of what you read about diet, anything, we do not exactly reproduce.

And lastly, smoking. You hear about smoking, and people are sick and tired of hearing about smoking because everyone knows that smoking is bad for you, but it is really bad for you, really bad for you, and the more often it is said, it does not matter, because it just is the big killer. Only 20% of people smoke now. In the old days, it was 60-70%. Well, women never - women got up to 50%. Smoking rates are going down, and that is really good, but still, overall, about 20% of cancers or 20% of excess mortality in the UK is in smokers. What you can see... This is numbers of cigarettes per day... This is never-smoked... This is the same sort of idea. This is people who smoke, women who smoke ten cigarettes a day, seems like not much, have double the risk of dying than people who do not, so double, just with ten cigarettes a day. I have talked about the pill and things, like it might be a 20% increase. This is a 100% increase - double. If women smoked twenty cigarettes a day, it is almost a four-fold increase. These are very large effects. There was an idea that maybe women smokers, it was not so bad in women or something, but for women because in our cohort, remember, women were sort of 56 when they started, the ones who were current smokers, and they had started smoking, on average, at about age eighteen, these are people who had smoked for about 40 years, 40 years of smoking is really not good.

But the important thing again, and it is a bit complicated to explain but I am going to say that...remember I said it was about double, the relative risk was about two if you smoked ten cigarettes a day, and four if you smoked twenty, but the average consumption is about fifteen a day, with an increase of three, so that there was, in all current smokers in the study, there was a three-fold increase in deaths from all causes. This is never-smokers, down here... But if you look at the age when people - and ex-smokers, this is ex-smokers down here...the age when they stopped, women who had stopped smoking, say had started but stopped smoking just in their early-20s, they really did not have an increase in mortality. So, having started but stopped in your 20s, really, there is almost nothing. When we look at lung cancer, there is still a tiny increase in lung cancer mortality even you stopped at twenty, but effectively, stopping at twenty or in your twenties takes away any of the excess risk if you continue. Stopping even at 30, which many people do, and people, at 30, people’s lives are much more sort of settled at 30, and even if they smoke, I mean, but to stop at 30, instead of a 200% increase, it’s a 5% increase. It is actually significant. The numbers are big enough to say this increase, even at 30, even stopped at 30, you have got a higher death rate in your 50s and 60s than people who never smoked, but you have lost some sort of 97% of the excess risk if you continue. Even stopping at 40, instead of being about 200-fold, there’s a 20% increased risk, so you have lost 90% of the effect of continuing.

So, you can hear the message through everything I am saying: what you do does have an effect. If you stop smoking, even if you stop at 50, you still do quite well. So, stopping smoking now, if you are a smoker, it will benefit you, and benefit you quite quickly. Losing some weight now will benefit you. If you did take HRT, stopping it, you go back to the same risk as if you had never taken it after a couple of years. So, that is really I think the main message that I want to leave you with: the risks...behaviour does not have as long term effects and as persistent effects I think as many people believe, and so it is sort of good news, that most of the things that we know about that are harmful, if you change what you do, it will affect the disease.

Thanks very much.

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28 May 2014

The Million Women Study
Thanks to the audience for coming. The title was a little bit dull, “The Million Women Study”, but what I am really going to talk about, which is important, is one of the reasons the study was set up was to look at questions, look at behaviours, normal sorts of behaviours, what women do, to ask the question: what can women do to stay healthy? Every day, there is not just one article or something in the newspaper or on the internet; there are usually lots and lots saying: if you run, you will not get dementia; if you drink orange juice, you will not get breast cancer, etc. etc. The interesting thing is that the public have quite a strong sense that a lot of this stuff probably is not true. It is interesting how people do not disregard a lot of things that they read, and rightly so, because often people do quite small studies and look at some little sub-group and find something that they think is very newsworthy and rather push that, and what I think I have tried to do in my life is to try and really be real about things and really to just understand and be really clear when one says...what was said today, and is right actually: even if you lose a little bit of weight, it is good for you, and that is true. So I am going to talk about things that we really know about, and the reason we know about it is combinations based on large numbers, reliable data, not nit-picking through things to see if we can find something that might sound very interesting in the short term. So, that is really what I am going to emphasise, and that is really why I started the Million Women Study, and I will talk about that - I will get there.

I am going to be looking at questions such as what are the effects on health of major lifestyles? And I am going to talk about lifestyle factors that you can potentially modify. Although it is not a lifestyle factor, one of the things we found is that the taller you are, the more likely you are to get cancer. Now, that is interesting in a biological way, but you cannot do anything about your height, so it is not in the same...and I am not going to talk about things that are not modifiable, or potentially modifiable here.

Now, you will see that it is very important to know the effects of some lifestyle factors, say smoking. I am going to talk about the pill, hormone replacement therapy, obesity, adiposity, physical activity, alcohol, diet, smoking - these are things you hear about all the time. It is really important to know whether effects are persistent or not because you only, for example, take the pill - women only take the pill for a short part of their life, when they are in their twenties, thirties, usually. HRT, women take at a different age. So, you have to ask: does it matter if these drugs, if they have an effect, does it persist or not? So I am going to talk about that a bit, and I am also going to just talk about the magnitude of effects - what are the big things and what are the little things? I am going to talk mostly about things that you hear about on the news etc.

I’m going to start with talking about conditions that are important, that people know about, that everyone in the audience here will know about, things that you read about – heart disease, hip fracture, which is a manifestation of osteoporosis, breast cancer, and venous thrombosis. The first thing that is really important to understand about all these conditions is that they each have a very characteristic age pattern. I will start with venous thrombosis, or thrombosis, often people call it, which you all know is associated with the pill and I will talk about it in a minute, but you see, for women in their twenties and thirties, thrombosis in the legs that can cause a pulmonary embolism – it is a clot that can occur in the legs and actually go into the lungs and people can die from it. You see, for women in their twenties and thirties, it is more common than breast cancer, heart disease and all sorts of other things, which is why, in a way, there has been so much emphasis on thrombosis and clots and women on the pill. It is because it, in young women, it does occur, whereas heart disease hardly occurs at all, and breast cancer really does not pick up until about the forties, but breast cancer does not increase as you get past fifties. Breast cancer is the most common - women in their forties and fifties - condition, but by the time you get to sixties and seventies, heart disease takes over. So, all these things are very important when you think about specific effects of different things and what you should be thinking about in terms of disease and what can happen, and as I said, and also what is persistent or not.

Now, you can see how hip fracture in yellowish goes up very rapidly with age, much more rapidly than say heart disease. Heart disease is going up quite a lot, but then hip fracture, osteoporosis, goes up much faster and overtakes heart disease. And dementia, which we are starting to work on and it is very important, dementia is pretty well unknown before about age 70, not entirely, and it just takes off and overtakes everything, but really sort of late-80s, 90s, so that issues to do with dementia become important later. But one has to ask, is something - these sorts of questions: is there something you can do in your 50s that will prevent dementia, or is it something you should be doing in your 70s? Are there persistent effects? It is those sorts of questions. So, age is really important in trying to understand the effects of many of these exposures.
I have already mentioned the pill and the fact that we all, again, read in the paper, clots, and that one pill is worse than the other pill and so forth, but it is right, the thing that one should be concerned about for the pill is really blood clots because that is what is more common in younger women, unless there is a persistent effect of something that is adverse.

But you see, hormone replacement therapy, as people usually call it, although the word “replacement” has gone now because I think it was always a silly word and it does not replace anything – well, it might, but it is an idea that was pushed, and this idea that it was replacing things that went wrong after the menopause is not necessarily right, but anyway, I am using HRT because people know the words.

You can see that, at the age when women take HRT, which is in their fifties and sixties, it is breast cancer, particularly women in their fifties, and heart disease are the biggest issues, so I want you to think about these things. As I have said disease rates vary by age. So do lifestyle factors and behaviours vary by age, and one has to ask what are the effects and whether they persist or not because that is really important in trying to understand the short term and long term effects.

I am going to start with the pill because actually this is how my career started and maybe, I do not know whether you in the audience are so interested in the pill, but there was a time – the pill came out in the ‘60s and it is, although people forget, it is the most widely used drug. 600 million women have used it, and there are 120 million currently using it, and interestingly now, there are far more women in sort of mid and low income countries using the pill than in high income countries. But if we think about high income countries today, I do not know whether this will surprise you or not but it sort of surprises me, that women, if you look at women in their 60s now in the UK, about 80% have ever used the pill, and for an average of seven years, so it is quite a long time, and women who are 90 today, 30% have used the pill for an average of about five years. So, there has really been not only “Is it so widely used?” but now really women of all ages have used it and so there are questions again. And there has been a massive amount of research, more than probably on any other drug, I will call it for these purposes, and we do really know a lot about it.

The interesting thing is, if you go back in the ‘60s and ‘70s, the first adverse effects that were reported were all vascular, things to do with the circulation. The first, in 1961, a year after the pill came out, there were already reports in medical journals of people, young people on the pill with venous thrombosis or blood clots which were unexpected. By 1962, there were 26 cases reported to the FDA, the Food & Drug Administration in the US, and so already, within years of the pill being made available, there were already reports of adverse effects. Soon after, in ‘62, the first report of a stroke, and ‘64, the first report of coronary heart disease.

Now, what all the studies have shown, and there was a huge amount of work done in the ‘70s, late-‘60s and ‘70s really, that showed that there is a two to four fold increase in the risk of blood clots, maybe not so large, but not too different for stroke and heart disease. But the important thing is this line down the bottom, that these effects are reversible. When women stop taking the pill, there is no persistent risk, so it goes away. So, while there are risks, they are reversible and so, you have already seen but I will come back to it, venous thrombosis is commonish, but pretty rare when you compare it with other ages, but the most common condition in women who take the pill, as a background rate, and people who are not on the pill but at the age groups that take the pill, is venous thrombosis. So, that is what should be the main concern and it still is.

But you see, the interesting thing is, when the pill was first marketed, and there had been a couple of studies, there had been some little – well, I would call them little, but they called them large then – studies in Puerto Rico of women given the pill. There was a bit of a worry that there may be cancer risks, and actually, cancer, when the pill was first marketed, it was cancer people were worried about and not vascular disease. But in the ‘80s and ‘90s, the emphasis did turn to cancer and there were a huge controversy. Again, some of you might remember – it is interesting just looking back in time. I cannot think of an equivalent controversy at the moment. So, there was a huge furor in the late-1980s about whether the pill caused breast cancer, and some people said it did and some people said it did not, and there were big arguments, big scientific arguments. I am just trying to think of an equivalent thing today and I cannot immediately think of how heated it was. There was something in the paper all the time, someone claiming one thing and the other thing.
I went to Oxford at the end of the ’80s really, in 1989, and it was really clear that someone had to sort out what was going on by actually bringing all the warring parties, you could call them, together, and just asking everyone to put in their original data and to merge it and to see what was going on. We set up this collaborative group on hormonal factors in breast cancer, and we set up in Oxford and we have meetings every five years – it still continues. The first results were published in 1996. Now, I am going to be showing probably more detailed results than you need to see, but just you can listen to me if you do not want to look at the figures. But what we found was really unexpected. Time is on this axis here, and this is like comparison with never-users of oral contraceptives. If there were points down here where main pill users did better than never-users, up there, they did worse. We found that people who were taking the pill had a relative risk of 1.2, which means about a 20% increased risk of breast cancer when they were taking it, and this is after years of stopping, and by ten years after stopping, this risk had gone away, so that the worst – and this was very unexpected because people generally think of cancer being caused something you do now and it has its effect a long time later, but what we found – but there is actually not as much reason to back up the idea that cancer is caused by long term exposures to things. Although it is a commonly held view, but it is not true, and a lot of the work that we have done has shown it is not true. So, very unexpectedly, we found, when you put the worldwide evidence together – this is from about 50 studies, about 50,000 women with breast cancer – we found that there was an increased risk, 20% increased risk, while people were taking it, and a few years after stopping, that had gone after about ten years. It was very clear and all the divergent studies all fit in once the basic pattern had been clarified, and so the studies were not disagreeing. It was just that people who were looking at older women, who had stopped the pill long ago, were saying there was not an increase, and people who were looking at younger women who were still on the pill were saying there was an increase, but there was no difference across studies. That was really a terribly important finding, really clear, and that this excess risk of breast cancer is reversible, and you now never, ever hear in the press, after we published this in ’96, there’s no discussion anymore about the pill and breast cancer. It is widely accepted that is what it is.

We have also done the same thing for cancers of the ovary and endometrium, and I think what I said before is, if you look down here, so this is never-users of the pill, actually, cancer of the ovary is reduced in pill-takers, as is cancer of the endometrium, the lining of the uterus. So that, contrary to breast cancer, the other sort of cancers in women that are hormonal, related to hormones obviously, to reproduction or organs of reproduction, the pill actually protects. This is the length that the pill has been used. The longer people have taken the pill, the greater the protection. You cannot see this, but these are different lines on when people stop taking the pill, and essentially, quite different from breast cancer, the pill protects against ovary cancer and cancer of the endometrium, or the lining of the womb, and it’s a persistent effect. Now, no one could have guessed this. We did the same thing of bringing together the worldwide evidence, and until you have all the data together and you make sure, and again, there was not any variation between studies, and there was not variation between some sub-groups. Some published…you hear, if you eat cereal and you take the pill, you are more likely to get this or something, but once you bring all the data together and you look inside, a lot of these sort of little sub-groups, effects that seemed sensational at the time, go away. So, this is what we found, and I am leading into the Million Women Study now, but you see, 50 years of research has taught us about the pill, and really a huge amount of research.

As I have already said, while the pill is being used, there is an increased incidence of vascular disease and also breast cancer, but these effects are reversible – there is no persistent effect. And because most of the serious illnesses in women, like breast cancer, cancer of the ovary, heart attack and everything, are rare in women in their 20s and 30s, except perhaps venous thrombosis that we have talked about, the numbers who have adverse pill-associated illness is very small. I mean, I have not gone through the absolute rates, but this is like one in 100,000 per year or one in – very, very small risks. So, although there is an increase in conditions that we have talked about, the excess risks, it is unusual to suffer from these side-effects.

In the long term, what we have is a persistent decrease in cancer of the ovary and the womb, and where we are now is that, in the long term, women who have taken the pill, they have a net reduction in cancer incidence. So, actually, and there is no one that pushes this idea very strongly, but really, I mean, women who have taken the pill are at a reduced, in terms of their cumulative risk, a reduced risk of cancer, and it really is something that one can say quite, I mean, it is true. And, you know, there is so much “What can we do for cancer prevention?” but it is interesting that people are very nervous of saying “Take the pill” – it is very interesting, is it not?

Anyway, now, HRT. When we were bringing together all the data I showed you on the pill and breast cancer, it was really clear that HRT, there was quite a hazard of breast cancer in people on HRT. Most of the data – this, remember, was in the sort of early-’90s – most of the data at that time came from the US. There was not so much use of HRT in the UK at the time. The sort of HRT being used in the UK was not the same as in the US, and also it was clear just from what was going on that HRT use was rocketing in women in the UK. So, we decided that we really needed to do a study looking at the association between HRT and breast cancer because, as you
can see, most of the users of HRT were women after the menopause in their 50s and it really was breast cancer that was looking quite worrisome. There had been a trial looking at heart disease as well, women in the US, and I will talk about that, but they are the two conditions I am going to talk about as far as HRT is concerned.

The women who were screened for breast cancer at that time were women in their fifties and sixties and we asked the screening centres – and I am going to say a bit about screening in a minute, but there are about 100 divisions in England, Scotland and Wales, which 100 – there used to be, I think, not regional health, some health authorities, and in every one of those regions, there was a centre where the spots are, but not all of them have got spots. There were about 100 centres that ran breast screening through the country, responsible for each of those areas, and the ones with the dots in them are the ones that took part. These ones did not, some areas. So, we asked each of the centres separately, and if they agreed, they put a study questionnaire in the envelope when women were invited for screening, and women were asked to fill out the questionnaire if they wanted to, they could – we were interested in HRT and breast cancer, but women’s health in general, and they could fill out a questionnaire, and it was handed in separately from the screening programme because we had to show that we were not in any way changing the way the screening programme ran because it was a very efficient organisation and we did not want to change that. So, over about a five year period, ’96 to 2001, we managed to recruit 1.3 million women who were 50-64 – that was the age that was screened then – which was about one in four of all women in the UK actually who were aged 50-60 at the time, and it was about one in two in the areas that we covered.

I am quite sure that some of you – if it is one in four women who are aged 50-64 at the time, I am quite sure some of you in the audience are part of that and we send you questionnaires from time to time, and it is very hard to say thank you in person to so many people, so I will say in person to you, and if this is recorded, I will say it to people who look at this over the internet as well, the study obviously would not exist without you, and with the questions. I think people often think how can these rather simple questions really help, but we do a lot of repeat – you might have got the same questionnaire again, where we ask the same question later and look at how well things agree, and actually, I think you would be surprised because, I think when you fill these questions in, you think, oh, I am just saying off the top of my head, but people tend to say the same thing over and over again. And we have got blood and we do all sorts of tests, so basically, the answers are much more reliable. It is more important to give a rough answer than to leave these blank if you are not sure and we always say that.

When women were recruited in the study, they were 56 on average. Now, 14 years later, they are 70, and that is why I think I said that we are starting to get interested and really want to do work – I started with the pill and HRT. We are going to start doing serious work on dementia next, but I am not talking about dementia now because women are just starting to develop dementia.

So, that is the Million Women Study, and we set out to look at breast cancer and hormone replacement therapy. Now, these are actually real rates. This is, in 1,000 women over a five year period, and it shows you how common breast cancer is, so much more common than cancer of the ovaries…still, it does. Breast cancer in never-users is so much more common than the other two cancers. So, if you have even a small effect on breast cancer in terms of how common it is, it affects large numbers of people.

I had said before that the type of HRT used by women in the UK was not the same as in the US. In the US, most of the HRT users just had oestrogens in them, but in the UK, what had been shown before was that HRT containing oestrogens only increased the risk of cancer of the womb, cancer of the endometrium, which was known about. So, in the UK, much more than the States, they said anyone who has got a womb should be given it. Instead of saying something else but they added something else – instead of just saying, “Well, maybe you should not take it,” or something, they said, well, let us put in another hormone, so you have got oestrogen plus progestagen, which, as you can see, women who are taking oestrogen plus progestagen – and this is much more used in Europe and the UK than in the US – so women, it is true that women who took oestrogen plus progestagen did not have an increase in cancer of the endometrium, whereas they did if they had oestrogen only. But little did the gynaecologists know that what they were doing by adding progestagen is increasing the risks of breast cancer really quite substantially. Ovary cancer, although the numbers look very small, is slightly increased in pill users, but it is small. You can really see that, when you put all the sort of hormone-related cancers together, it is breast cancer that predominates. And as I was saying, if you put them all together, in five years, about 20 women in a 1,000, so two in a 100, will get one of these cancers, over a five year period – this is women in their 50s and early-60s. So, it is not a small number, 2%, two in 100. If you take oestrogen plus progestagen, it goes up to over three, so it becomes 3% instead of 2%. Now, that means that one woman in 100 over a five year period, for every 100 taking HRT, one more is getting breast cancer. It is quite a big number. It is not a small number. As I said, the pill related things were in the one in 100,000. This is one in 100,
much bigger effects, and now studies in Europe have generally found exactly the same. As I said, in the States, this oestrogen-only tends to be used and it is not half as bad as adding the progestagen.

The other thing that we found, just as with the pill, that the excess risk, and this is like in the same format as I showed for the pill, that although there is an increase, much bigger, about 20% increase for the pill, current users of the pill, it is about a 70% increase, but again, after stopping, and here it seemed like four or five years after stopping, the risks were the same as never-users. So, the good news, and the important news, is it is reversible. The effects of HRT on breast cancer are reversible. So, although there is an increased risk, as with the pill, it seems to be a short-term effect.

Now, I am not going to talk about coronary. We are just analysing that now and these are results from the randomised trials that were done in America, as I said, at the same time about as we started the Million Women Study.

Basically, HRT use was increasing very rapidly during the ‘90s because it was widely said that women who took HRT, their risk of heart disease was reduced and that they would live longer and so forth, and all sorts of claims. But the randomised trials – I will not go through and explain this, but basically, it did not matter whether they were taking oestrogen-only or oestrogen plus progestagen, there was really little evidence – there was certainly no decrease in risk, and not much to say there was an increase. The MHRA, which is like our FDA equivalent here, they said there is no evidence, because some people argue, if you start when you are very young, it is beneficial, but there is really not much evidence to say it is beneficial. Anyway, so we published on breast cancer and the trials in the US published about the same time around – the trials in the US published 2002, and we published our results on breast cancer in 2003.

You can see this extraordinary thing that happened in the UK. In a very short – since about the mid-’80s, use of HRT went from almost no one to 2.5 million users in the UK, but with the results particularly of the trial showing there was not a benefit of cardiovascular disease, and possibly, they said possible decrease, and others showing increase in breast cancer, there has been this rapid decline. It has not gone away completely, and actually, we have got some even more recent figures, and it looks as if it is levelling off, so it has not gone down at all. So, there is still about a million users of HRT in the country, but it is interesting to see how rapidly and how the public actually realised this was real. And, I said before that a lot of the findings that you hear about in the media and so forth, people do not react to, but they reacted to this very well, and I think that people who read the papers, listen to things, seem to know the difference between reality and what is real and what is hype, and this was real. It is particularly breast cancer that is the problem, and it is just interesting to see how rapidly use fell, and also showing that it was not the elixir of youth or whatever it was sold as.

What has been published since then – and I said it is reversible, the effects – the drop in HRT use, this is a bit complicated, you do not have to see this. This is data from the States, where use of HRT fell very quickly, and breast cancer incidence fell, and it was particularly breast cancers that are responsive, that are called oestrogen, with oestrogen receptors, and that has been in a dozen countries now, so that, following this drop in use of HRT, breast cancer rates have dropped slightly in women in their 50s and 60s.

Interestingly enough, I will just show this and not say anything about it, but coincident with the drop in HRT use, in the UK, and I presume – or this is data for England, but I presume it is true everywhere, many other places, there has been an increase, in prescription of drugs called bisphosphonates. I should have said actually, that HRT is very good for the bones and that there is a reduction in fractures and osteoporosis, but it is while women are taking HRT, but if you remember, it was women in their 80s who get osteoporosis, sort of late-70s and 80s, osteoporosis and fractures and problems with osteoporosis, and taking HRT when you’re 50 is not going to help osteoporosis when you are in your 70s and 80s. So, what has happened is these drugs called bisphosphonates have just taken over. I mean, it is very interesting how doctors want to prescribe something else. If you are not prescribing HRT, we will try something else, and I will tell you, we know almost nothing about what bisphosphonates do, and that is another thing that we are planning to do in the future. But they have taken over from HRT...

I just want to say, although I have not done work on this, but we did recruit through the screening centres, and that is why there has been a lot of fuss about in the media lately – you have probably read that, and actually, I know from attendance figures that people have pretty well ignored all the fuss because there has been a lobby
saying that breast screening does not work and you should not go and it does more harm than good. Well, it is just not true. There was a big review – and there have been a dozen trials. This is just to show you that there have been different trials, in the USA, Sweden, UK, Canada, Finland, all these trials randomising people screened or not have shown benefits. There has been a lot in the media about that, and finally the Government set-up an independent review, and they said, yes, it does save lives, there have been 1,400 fewer deaths from breast cancer in England every year because of screening. I just want to say – it is not my research – but it is not a behaviour either, but screening does work and does reduce deaths from breast cancer, and there’s not much we can do otherwise about breast cancer, so it is important.

If people have very bad menopausal symptoms, and that is what the MHRA, I was going to say, the FDA-equivalent, says, if you want to, you should take HRT for as short a time as possible for severe, for real symptoms. But there is a bit of a movement now with the drug company and people who made a nice living out of HRT beginning to try and say, oh, all the evidence was wrong, ten years ago, ignore everything that has happened and go back to HRT. There is quite a push. It is interesting, all these lobbies, as I said, there has been an anti-screening lobby, there is a growing pro-HRT lobby. But, as I say, I think people are very sensitive to all these things.

As I said, we heard today’s news event is, if you lose a little bit of weight, it is good, and the answer is that is right. Now, all of this is a bit too much. I am not going to go through this in detail, because the study is so big, out of the 1.3 million, there are about 100,000 women who have developed cancer of some sort, and so we have a lot of statistical power where we can just see exactly what does and this is a 10 unit increase in BMI. It is like being from normal weight to obese. So, if you go from normalish weight to obese, what happens to cancer risks? We have taken the 18 most common cancers here. I am not going to go through them all. But if there is a square on this side, it means obesity is bad for you; if there is a square on this side, it means it is good for you. Now, for most of the cancers, and particularly the endometrium, which I have talked about a lot, cancer of the womb, the difference between a normal weight woman and someone who is obese, the obese woman is 2.8, almost three times as likely to get endometrial cancer, and so forth and so forth. I am not going to go through them all. Smaller effects for some things, but nine out of the 18, down to here, there is all significant increases with obesity. Some of the ones, there is no effect with obesity, and two really, cancer of the lung and squamous cell, one of the cancers of the throat, there is a decreased risk. But mostly, being obese is not good for most things. It is good for just a few things, a very small number of things.

It is much worse for other things though. This is for non-cancer risks. We took the 25 most common conditions women are admitted to hospital for, and for 21 out of the 25, being obese was a bad thing, topped by, as you all know, diabetes, but the second, again which people do not know so well, is knee replacements. The magnitude of the effect of obesity is almost as bad as for diabetes. Women who are obese are much more likely to have to have a knee replacement, have knee problems. Venous thrombosis is quite high, and gallbladder disease, carpal tunnel syndrome, atrial fibrillation, hip replacements, these things are all more common. Ischaemic heart disease, down here, which you hear about. I have not shown all the list, but again, obesity is bad for most things. It is good for just a few things, a very small number of things.

People who are morbidly obese are eight times more likely to get endometrial cancer of the womb than normal weight women. But the next slide...so this just shows you...and there is a linear relationship: the more obese you are, the greater the risk.

The next slide is a bit complicated and I am just going to tell you what it shows because it is a little bit hard and I am sorry about this. This shows what your body size was - we asked people and we have been able to validate and show that this was true when we have got actual measurements of people. People who were thin, and average, or plump, when they were ten, and this is what they were when they were ten, and these things are what their BMI is now, what they are now, and this is saying women who are not overweight, who are normal weight now, in their 50s and 60s, it did not really matter – their endometrial cancer risk did not really matter, it did not matter whether they were thin, average or plump when they were ten. So people who are obese now, it did not matter if they were thin, average or plump when they were ten, and similarly people who are in what is called the overweight group, did not matter if they were thin, average or plump. So, what this is saying, and really important, is that it is what you weight now that is important. There does not seem to be a persistent effect from the past. There is a persistent effect, you can say, that most people who were plump when they were young end up plump when they are older, but if you look within strata and hold these things constant, it looks as if there is not much effect on endometrial cancer and on the other cancers we have looked at what you were when you were younger. And this is, you know, the extremes are here...like if you are lean at 10 and obese at 60, you are the same as if you were plump at 10 and obese at 60, and these are people who were plump at 10 but lean at 60 and they are the same. So, the extension of this is it is what you are now that matters. And, in
a way, it is also implying these things are reversible. What happens to you at a certain age, if you get to 60, it is what you are at 60 that matters, not what you were when you were 10. So, it is a bit of a similar sort of message to the pill or HRT, that really, it is what you do now that matters, and so that is why what I said was right, what was in the news today, losing some weight now can help you because it is what you are now that is important, and that, I think, should be seen as quite a relief to people, that you can still change – if you change your behaviour now, if you change your weight now, it is worthwhile.

Physical activity matters, but it matters in different ways for different conditions. We have just looked at fractures, for example. These are people who were active. For hip fracture, the more active you were when you filled out the questionnaire, the more active you were, and we then followed people to see if they had hip fractures. Being active was very good for hip fractures. But interestingly enough, for ankle fractures, and for wrist fractures too, if anything, there was no effect, or even a slight increase, and I think that, again, if you are more active, you can fall over more, but the very serious hip fractures, you are protected against, presumably, for all sorts of reasons. But it is just to say that it is not always the same for every condition, and not all fractures are the same.

Now, we have just got this result, which we have not published yet, and it is a bit curious, but we have also looked at physical activity and vascular disease. This is heart disease, this is stroke, and this is blood clots, venous thromboembolism, and this is quite curious in that people who are pretty well inactive – and this is strenuous activity, so they rarely or never do anything, compared with them, if you do some sort of activity once, up to once a week, two to three times a week, it is a very good thing, as one has heard, and that is true, but we do find this odd thing here, that the very active, being active more than three times a week, doing activities, there seems to be an increase in this. As I said, it is not published yet – curious and it may fit with, you often hear about people being very, very active and then having some catastrophic vascular event, and that might be what our data is showing too. But generally, for most people, physical activity is a good thing for heart disease and stroke, but maybe one should not overdo it.

Alcohol and diet. Now, I am just going to show you this. It is very important because there is a lot of talk about alcohol and cirrhosis. I think mortality from most conditions in the UK is falling, particularly from vascular disease, is falling very rapidly. Expectation of life is increasing very fast. But one of the few conditions where the incidence rates are really going up quite rapidly is cirrhosis of the liver, and it is not only alcohol. Women do not drink very much. The average, for women in general, is less than one drink a day. But for women who drink about one drink a day, they have got a significantly greater risk of cirrhosis, so one drink a day is enough to do this. Once you get to almost three, you can see, there are very big risks – they go up quite fast. But there is also a difference between non-obese and obese. At every level of alcohol consumption, obese people have higher rates of cirrhosis, and probably the reason cirrhosis is going up is a combination of people drinking more and being more obese, because rates are really going up very fast, and as I say, women do not drink much, but even at the very small levels, one drink a day, on average, two drinks a day, you can see the effects.

Now, I am going to say the same, alcohol also, if you do the same – I showed you this long plot, the different sorts of cancers, for obesity. If you look at alcohol, alcohol affects some cancers. It is not as great an effect as obesity, but the one that is really important, particularly for women, is it does increase breast cancer risk, and so it is 12% for 10g. This is grams a day I am talking about, not obesity – this is for one drink a day, on average. So, it is about a 12% increase for every drink. So compared with none, women who drink nothing, women who drink one drink a day on average have about a 12% higher risk of breast cancer, and if they do two drinks a day, it is 24 and so forth. Again, it is because breast cancer is really common in women this is quite an important result. But you will see, which others have reported too, that some cancers are reduced with alcohol, so it is not a totally simple picture. The size of these squares tells you something about how common the diseases are, and breast cancer really dominates the picture. We also found, I mean, as others have found, but basically, the cancers that are affected by alcohol are, not surprisingly, ones of the mouth, the larynx, the pharynx, the esophagus, the gullet, and the liver. It is not surprising, the ones that are increased, and most of the other cancers are not increased.

Oh, and just to say that it does not matter – this just shows people who just drink only wine, or other mixtures. It does not matter. It is the same – it does not matter where the alcohol comes from, the effects are the same.

Diet and fibre. I am just going to show you one slide that we have got - diverticular disease of the bowel is a condition where, in the colon, you get little pockets that can get infected and cause all sorts of abdominal
problems. We really found a strong association, the more fibre you ate, the less likely that was to be. But we are actually having trouble finding, or reproducing what other people have found about diet, so that, if I just say, for the moment, that much of what you read about diet, anything, we do not exactly reproduce.

And lastly, smoking. You hear about smoking, and people are sick and tired of hearing about smoking because everyone knows that smoking is bad for you, but it is really bad for you, really bad for you, and the more often it is said, it does not matter, because it just is the big killer. Only 20% of people smoke now. In the old days, it was 60-70%. Well, women never – women got up to 50%. Smoking rates are going down, and that is really good, but still, overall, about 20% of cancers or 20% of excess mortality in the UK is in smokers. What you can see... This is numbers of cigarettes per day... This is never-smoked... This is the same sort of idea. This is people who smoke, women who smoke ten cigarettes a day, seems like not much, have double the risk of dying than people who do not, just with ten cigarettes a day. I have talked about the pill and things, like it might be a 20% increase. This is a 100% increase - double. If women smoked twenty cigarettes a day, it is almost a four-fold increase. These are very large effects. There was an idea that maybe women smokers, it was not so bad in women or something, but for women because in our cohort, remember, women were sort of 56 when they started, the ones who were current smokers, and they had started smoking, on average, at about age eighteen, these are people who had smoked for about 40 years, 40 years of smoking is really not good.

But the important thing again, and it is a bit complicated to explain but I am going to say that...remember I said it was about double, the relative risk was about two if you smoked ten cigarettes a day, and four if you smoked twenty, but the average consumption is about fifteen a day, with an increase of three, so that there was, in all current smokers in the study, there was a three-fold increase in deaths from all causes. This is never-smokers, down here... But if you look at the age when people - and ex-smokers, this is ex-smokers down here...the age when they stopped, women who had stopped smoking, say had started but stopped smoking just in their early-20s, they really did not have an increase in mortality. So, having started but stopped in your 20s, really, there is almost nothing. When we look at lung cancer, there is still a tiny increase in lung cancer mortality even you stopped at twenty, but effectively, stopping at twenty or in your twenties takes away any of the excess risk if you continue. Stopping even at 30, which many people do, and people, at 30, people's lives are much more sort of settled at 30, and even if they smoke, I mean, but to stop at 30, instead of a 200% increase, it's a 5% increase. It is actually significant. The numbers are big enough to say this increase, even at 30, even stopped at 30, you have got a higher death rate in your 50s and 60s than people who never smoked, but you have lost some sort of 97% of the excess risk if you continue. Even stopping at 40, instead of being about 200-fold, there's a 20% increased risk, so you have lost 90% of the effect of continuing.

So, you can hear the message through everything I am saying: what you do does have an effect. If you stop smoking, even if you stop at 50, you still do quite well. So, stopping smoking now, if you are a smoker, it will benefit you, and benefit you quite quickly. Losing some weight now will benefit you. If you did take HRT, stopping it, you go back to the same risk as if you had never taken it after a couple of years. So, that is really I think the main message that I want to leave you with: the risks...behaviour does not have as long term effects and as persistent effects I think as many people believe, and so it is sort of good news, that most of the things that we know about that are harmful, if you change what you do, it will affect the disease.

Thanks very much.