

Why is cancer killing more men than women?

→ Marc Beishon

A rising focus on men's health issues, more sophisticated registry data and new techniques for investigating the biology of cancers are fuelling interest in unravelling what lies behind gender differences in cancer incidence and mortality. Getting answers could boost prevention and early detection and could even lead to better targeted therapies.

When it comes to the differences between men and women, publicity about cancer tends to focus on the tumours specific to each sex – in the main, prostate and testicular for men and cervical, ovarian and breast for women (although of course men also get breast cancer – and there is rising incidence in some countries). But there are striking differences between adult men and women in some cancers common to both sexes, which are starting to receive more attention – and which raise a wide range of biological, social and environmental issues concerning cancer incidence, survival and mortality.

As Jan Willem Coebergh, professor of cancer surveillance at the Department of Public Health, Erasmus Medical Centre in Rotterdam, points out, there are two cancer sites which currently stand out as significantly different in cancer survival and which are hard to explain. Melanoma

has a higher incidence in women, but more men proportionately die from the disease. But the reverse is true in bladder cancer, where the prognosis for women is poorer despite a lower incidence. Trying to unpick the reasons for these disparities can involve everything on the 'gender' side, from when men and women present to health services, to what doctors do that may be different, to lifestyle risk factors such as smoking and obesity, and also the 'sex' factors – possible differences in male and female biology.

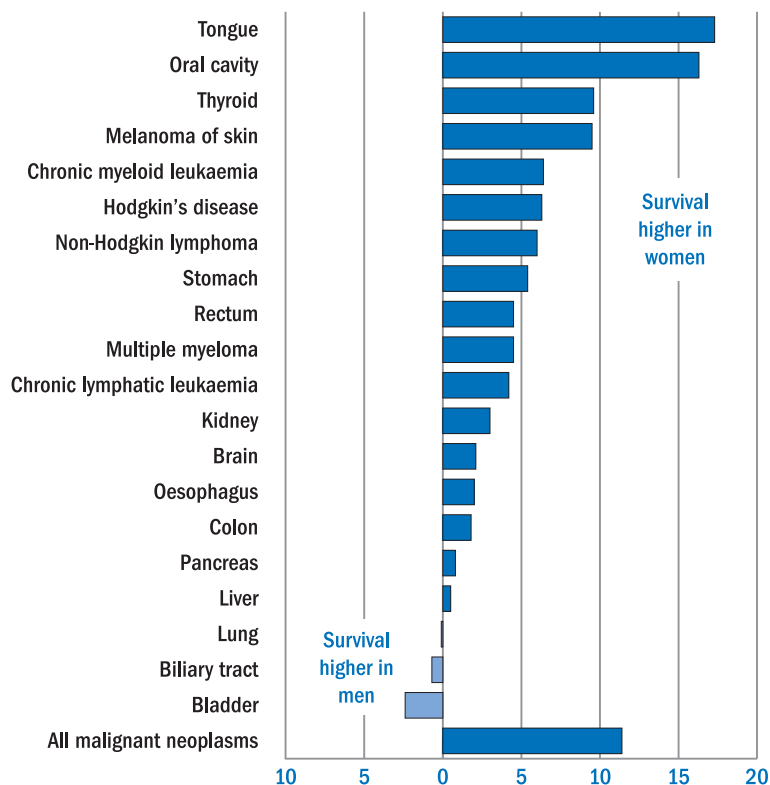
However, for some cancers common to men and women the big differences, in incidence at least, are relatively straightforward to explain, according to Coebergh. "Tobacco exposure in particular and also alcohol explain the higher rates in men in many countries in tumour sites such as lung, larynx, bladder and to some extent pancreas, and we have of course seen a decline in these cancers in northern Europe as smoking rates have decreased, although there is a

lag of 0–25 years in the data." As male and female smoking rates have become more equal across Europe, so too has the cancer incidence difference narrowed in those tumours where tobacco is a major risk factor.

"We are also seeing the rates of colorectal cancer in older men going up in some countries – this could be the result of a longer latency time of 30–40 years for smoking, but the data is much less robust," he adds. He points out that survival and mortality rates in older age groups are also heavily influenced by comorbidity with other diseases, especially cardiovascular conditions and chronic obstructive pulmonary disease – again where smoking makes a major impact.

But as Coebergh adds, the wider statistical picture of male and female differences around Europe is very mixed and complex. An analysis of the latest Eurocare-4 data shows that, for Europe as a whole, the regionally weighted mean

DIFFERENCE IN RELATIVE SURVIVAL (%) BETWEEN WOMEN AND MEN



Age-standardised data for adults diagnosed in the period 1990–1994.

Source: MP Coleman et al, *Eurocare-3 Summary, Ann Oncol 2003, vol 14 (suppl 5), v135*

UNRAVELLING THE CAUSES

It has been ten years since Micheli et al published their last gender paper, which looked at earlier Eurocare data. In ‘The prognostic role of gender in survival of adult cancer patients’ (*EJC* 1998, 34:2271–78), which was put forward as the first such examination of gender in cancer survival, they suggested that “women may be intrinsically more robust than men in coping with cancer.” The better overall survival in women, they noted, could result from one or more factors – women paying more attention to their bodies, resulting in earlier diagnosis; the impact of different risk factors on the cancer case mix; and a “biological superiority in women in responding to disease, treatment or both”. They also note the figures may be skewed by different corrections for comorbidity between men and women.

For Alan White, probably the first professor of men’s health in any country, based at Leeds Metropolitan University in the UK, the data on worse incidence and outcomes for many male cancers is a huge issue that absolutely requires more detailed analysis. “In 2003 the European Men’s Health Forum commissioned a study of men’s health across Europe, the first time we had looked across all health issues for men, and it emerged that men seemed to be developing and dying from all sorts of conditions at a greater rate than we thought. We assumed that cardiovascular disease would be the major condition – but cancer emerged as a higher cause than we anticipated.”

White has also assembled data from various sources. Looking for example at the differences in England and Wales between the sexes he finds that, although cancer accounts for a greater proportion of female deaths in younger age groups, removing breast and genital cancers reveals that “63% more men in England and Wales in the 15–64 age group succumb to cancers that should be affecting men and women equally”.

five-year cancer survival is about 55% for women, but just 45% for men for all tumours, and those countries that spend the least on healthcare per head have notably lower scores.

It is notable too that the US has much higher survival figures than Europe and men actually do better – about 66% for men and 63% for women. But as Franco Berrino and Riccardo Capocaccia point out, in *Responding to the challenge of cancer in Europe* (available from WHO Europe), men in the US have a lower incidence of lethal cancers such as lung and stomach, and an exceptionally high incidence and survival for prostate cancer, thanks to widespread screening.

Those wanting to delve deeper into gender patterns could look at a recent paper in the *European Journal of Cancer* (Henrike Karim-Kos et al, 2008, 44:1345–89), in which Eurocare and other sources are mined for 17 cancer types across Europe. This lengthy report gives detailed figures for men and women on incidence, survival and mortality for several cancers, including colorectal, pancreatic and lung, and summaries of trends in various countries. There is also some discussion on possible reasons for the gender patterns. A more detailed gender paper, by Andrea Micheli and colleagues at the Eurochip health indicator project in Milan, will be published in the *EJC* this year.

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He has since spent a good deal of time analysing the causes for the excess male cancer mortality, including organising an expert symposium on the issue (“Tackling the excess incidence of cancer in men”), held in 2006 in Leeds. At this event, David Forman, of the Centre for Epidemiology and Biostatistics at the University of Leeds, noted that the received wisdom of men presenting later is not sufficient to explain the discrepancy in mortality rates. He also commented that the drop in smoking among men and the lower rates of lung cancer, while cutting overall male rates could still mask differences in other cancers, and indeed in most other tumour sites there doesn’t appear to be any single explanation for the higher incidence in men, though a simple combination of smoking and alcohol is associated with male oral cancers.

White considers that while later presentation is a factor, it has to be added in with a wide range of lifestyle factors including smoking, diet, physical exercise, body fat and obesity. Socioeconomic inequality also plays a part – in England, social disadvantage worsens outcomes for men more than for women. (The Eurocadet project – www.eurocadet.org – is currently examining the major lifestyle and socioeconomic factors affecting the incidence of cancer around Europe.)

Melanoma stands out, as Coebergh and White comment, because of the worse outcome for men coupled with lower incidence – one of the few cancers, in fact, where incidence is higher in women. Identifying the reasons may help point researchers in promising directions. At the Leeds expert symposium, Forman presented data that showed that even after controlling for stage at presentation

and the location of the tumour, there is still a 31% survival advantage for women, which can partly but not wholly be explained by factors such as age and socioeconomic status. Similar results have been written up by colleagues of Coebergh in the Netherlands, led by Esther de Vries at the Erasmus Medical Centre, where again an unexplained gap in male/female survival was found in a sample of more than 10,000 Dutch melanoma patients.

“Hypotheses about the difference include looking at the role of the immune system,” comments Coebergh. “And there is also evidence about obesity as a cancer risk for men and melanoma – we do not see the same risk in obese women – so the underlying factors that determine obesity in men may also determine the progression of melanoma.” He points to a recent meta-analysis in the *Lancet* that reinforced the obesity link. He adds that his group is cooperating with the European Organisation for the Research and Treatment of Cancer (EORTC) in looking at melanoma trial data, where there is more detailed pathology, in the search for prognostic factors for men and women. Other research he mentions is led by Alan Spatz, chair of the EORTC melanoma group, on the role of the X and Y chromosomes in protection and tumour progression. “An interesting point is if we can explain the male/female difference it might lead to new therapeutic approaches, as nothing seems to work so far with melanoma.”

Meanwhile, in bladder cancer, which stands out as a cancer in which women face a worse prognosis, Coebergh says he is not aware of systematic efforts to explain the reasons, but there are various

explanations, including underlying biological causes, while urologists have, he says, traditionally investigated men earlier and more thoroughly than women, where in any case the tumour has been rare.

CULTURAL FACTORS

Differences in treatment and wider cultural factors are of great interest to White. “My concern is that we start seeing a marked rise in incidence of diseases such as cancer and heart disease after the age of 35 in men, which is also the time when they are least likely to be seen by health services. We need to target men more effectively in the workplace so that we can identify those men who are reluctant to come forward and are missing the benefits of early diagnosis.”

The European Men’s Health Forum (EMHF) leads on many activities like this around the region, and this year made the workplace the theme for the International Men’s Health Week. It issued a ‘Lung cancer in the workplace’ document in June, which highlights the need for health policies for migrant workers.

The EMHF’s president, Ian Banks, is a pioneer of men’s health in Europe, and now a visiting professor at Alan White’s department. The site www.emhf.org has copious resources, including a download of the proceedings of the Leeds expert symposium – this event, White is pleased to report, is referenced in England’s recent reform of its national cancer strategy. “It is clear that more research is needed if we are to fully understand how gender impacts on cancer,” the strategy notes.

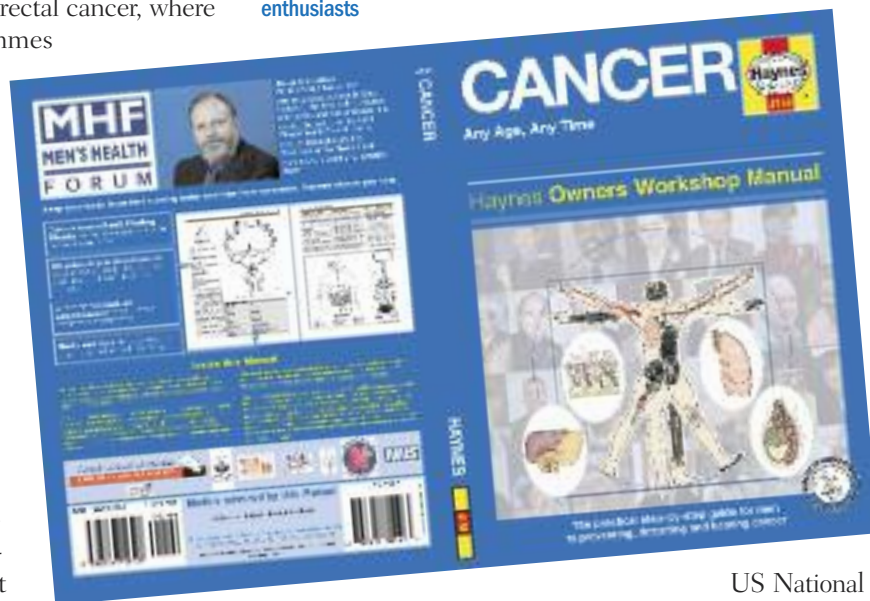
Indeed, the EMHF and professionals such as Banks and White are also calling for far more research about men and

cancer. As White says, “No systematic study of men’s increased risk of cancer has yet been undertaken.” There could, he adds, be major implications for healthcare policy makers in the sex and gender differences. Take colorectal cancer, where screening programmes

are now starting to be implemented in several countries: if there is evidence that men are developing and dying from the tumour earlier than women – which indeed there is – does it make sense to start everyone at the same age? It may be more effective and cost-effective to bring forward the age of first screening for men, or put back the first female screen.

Coebergh points to another factor with colorectal cancer, this time in favour of men. “Men tend to have spouses to look after them and so are more likely to receive adjuvant chemotherapy than women, many of whom are widows when they are diagnosed with disease.” Another intriguing difference in treatment applications, which was reported at the expert symposium, concerned oesophageal cancer, where data from one region in England show that radiotherapy is the favoured treatment for women with oesophageal cancer but chemotherapy for men. Marked differences have also been reported in surgery for colon and rectal cancers, and treatments offered for

Targeted message. To catch the attention of an adult male audience, the UK Men’s Health Forum published this information and advice on cancer in the form of a ‘Haynes manual’ – familiar to all car lovers and do-it-yourself enthusiasts



lung cancer. These differences are not easy to explain, although other patterns are, such as more aggressive treatments for younger men.

Response to treatment and fundamental differences in biology add further layers of complexity. Trials of new therapies will increasingly look for differences in how men and women respond as knowledge of genetic factors increases. Hormones, notes Coebergh, could also be playing a role in some cancers. Oestrogen, for example, while a risk factor in postmenopausal women for breast cancer, may be protective in sites such as the bowel and stomach where there are also oestrogen receptors. Studies have shown that exposing men to oestrogen can reduce their risk of gastric cancer, for example.

Researchers in the US have recently carried out one of the first studies on mice showing that male animals suffer more skin damage and worse tumours when exposed to harmful ultra-violet radiation.

But it is only relatively recently that a massive gender bias – in men’s favour – has started to be addressed in developing therapies. Many cancer drugs were initially tested only on men, and there is continuing bias in clinical trials and research towards men not just for cancer but for most diseases. Safety and comparability with other studies are among the reasons for women’s exclusion. In 1994, the

US National Institutes of Health issued guidelines that allowed American women to enter phase I, II and III trials, but as Anita Holdcroft, of Imperial College, London, writes, “there has not been a dramatic recruitment of women’s data into trial results,” and many drugs are withdrawn from the market because of women’s health issues (see *J R Soc Med* 2007, vol 100).

There is a good deal more to come in the sex and gender story in cancer, as there is in the development of ‘gender medicine’ as a specialty in its own right. Just where the biggest impacts are likely to come from – underlying biology, or cultural and treatment factors – and for which cancers, should occupy researchers for some time, provided the will and pressures are there to carry out the studies.

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